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ABDOMINAL SURGICAL EMERGENCIES CAUSED BY UREMIC ENTEROCOLITIS: REPORT OF TWELVE CASES*

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Although uremic enterocolitis is familiar to all physicians, it is generally unappreciated that this enterocolitis may be of a nature and severity to both produce and mimic acute surgical conditions of the abdomen. It is our purpose to illustrate these points of surgical interest by a review of twelve cases which occurred within the past two years of our experience at the Veterans Administration Hospital and the Grady Memorial Hospital. An illustrative case is presented in detail and the remaining cases are summarized (see table 1).

Case 1. A 30-year-old Negro assembly line worker on leave from another hospital, where he was under treatment for hypertension, was admitted because of the sudden onset of severe cramping periumbilical pain gradually progressing in severity and associated with watery diarrhea. The stools were initially green and then became bloody. There was no abdominal distention or anorexia. The pain persisted and was associated with tenesmus and flatulence. In addition there were progressive weakness, thirst, lethargy, night sweats and chilly sensations.

The past history was significant in that there was a known history of hypertension for 3½ years with clinically overt manifestations of headache and blurring of vision for 2 years. There was no past history of melena or of symptoms compatible with those of peptic ulcer. According to the patient's own statement, he had taken every known anti-hypertensive drug.

The temperature was 100°, respirations 18 per minute, pulse 130 per minute. Examination revealed a well developed, well nourished Negro man in no severe distress, alert, oriented and cooperative though complaining of abdominal pain. There were grade II changes in the fundi. The heart was enlarged and there was a protodiastolic gallop rhythm with a grade II systolic murmur over the entire precordium, loudest over the aortic area. There was no rigidity or distention of the abdomen although there was tenderness in the periumbilical region which interfered with adequate abdominal palpation. Diffuse rebound tenderness was present. The rectal examination revealed port-wine feces and no other abnormalities.

The total leukocyte count was 21,000 with a differential count of 6 bands, 77 neutrophils, 3 lymphocytes, 2 monocytes, and 1 eosinophil. The hemoglobin was 6.9 gm., hematocrit 23 mm., the urinalysis was normal except for a trace of albumin. Stool was guaiac positive; the VDRL was negative, and serum lipase was within normal limits. Stools were positive for occult blood until the 9th hospital day and then became negative for 10 days, and were then positive again. After six whole blood transfusions, the hematocrit stabilized in the range of 30 to 35 mm. On the 19th hospital day, the hemoglobin fell to 7.9 gm. Barium enema and gastrointestinal roentgenograms, and special small bowel studies were normal except for slight exaggeration of the mucosal folds in the jejunum. Sigmoidoscopy showed no abnormalities.

He was initially treated with antibiotics and after the 5th day, he became afebrile and symptomatically improved. There was a recurrence of abdominal pain, periumbilical tenderness, rebound tenderness, a slight temperature elevation, and guaiac positive stools.

Because of the continued bleeding, a laparotomy was performed. A 4-ft. length of lower jejunum was thickened and showed numerous areas, 4 to 6 cm. in diameter, without involvement of the serosa but suggesting localized hemorrhagic areas

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TABLE 1

Summary of 12 cases

Case	Age	Race	Clinical Manifestations	Gastrointestinal Findings	Renal Findings
1	30	N	Massive intestinal hemorrhage	Extensive ulcerations, arterolitis	Malignant arterial nephrosclerosis
2	37	N	Abdominal pain, nausea, vomiting; occult blood	Colon ulcers and hemorrhage	Nephrosclerosis and glomerulonephritis
3	25	N	Abdominal pain, rigidity, tenderness; occult blood	Small and large bowel uremic enterocolitis	Malignant arteriolar nephrosclerosis
4	28	N	Abdominal tenderness, cramping, sigmoidoscopy ulceration, rebound tenderness, ileus	Necrotic areas, small and large bowel; periarteritis	Periarteritis
5	44	W	Acute surgical abdomen; laparotomy	Extensive hemorrhagic enteritis	Myeloma nephrosis, extensive tubular damage
6	56	W	Abdominal distention, vomiting; rebound tenderness, occult blood	Fibrinopurulent areas of necrosis in ileum and colon	Amyloidosis
7	30	N	Abdominal pain, nausea, vomiting	Mucosal hemorrhages with sloughing, necrotizing arteriolitis, ileum	Severe arteriolar nephrosclerosis
8	33	N	Intermittent R.U.Q. pain; occult blood	Severe uremic gsatritis, moderate enterocolitis	Malignant arteriolar nephrosclerosis
9	54	N	Weight loss, constant abdominal pain, jaundice, ileus, leukocytosis, occult blood, diarrhea, hematemesis	Gastric ulceration, necrotizing vasculitis	Periarteritis
10	31	N	Sudden onset intermittent abdominal pain; bloody stools	Ulcerative uremic enterocolitis	Malignant arteriolar nephrosclerosis
11	50	N	G-I bleeding 10 days, lower abdominal pain, abdomen guarded, Hgb 5.1 gm.	Marked uremic gastritis, jejunitis, ileitis, colitis	Severe chronic pyelonephritis
12	75	W	Initial Dx:GI malignancy; pain, constipation, change in bowel habits, 50-pound weight loss	Petechial and submucosal hemorrhages, arteritis	Polyarteritis, chronic pyelonephritis

in the other layers of the bowel. No other intraperitoneal abnormalities were found. The involved portion of the bowel was resected and an end-to-end anastomosis was made. Except for a rise in blood pressure to 295/160, surgical convalescence was uneventful. However, within a short period, the blood urea nitrogen rose to 110 mg. per 100 cc. and the urinary output gradually diminished. He expired on the 11th hospital day.

At necropsy, the kidney showed malignant arterial nephrosclerosis. Beginning at a point 15 cm. above the site of the enterectomy, the jejunum was irregularly indurated, thickened, edematous, and marked by scattered ecchymotic hemorrhages beneath the serosa. This extended throughout the jejunum and ileum and erratically involved the cecum, ascending and transverse segments of the colon. The mucosa throughout was markedly redundant and edematous; scattered over the surface were confluent aggregates of myriad small friable granular polypoid areas of hemorrhagic and necrotic tissue. These were spread about all over the mucosal surface of the bowel without orientation toward the vessels and in some places were confluent. Some of these areas were sloughing with the formation of shallow ulcers. The mucosa that was yet viable was marked by scattered petechial hemorrhages. This process was best developed in the jejunum and upper ileum becoming less well developed in the lower ileum until in the cecum and colon there were only scattered areas of ulceration. Mesenteric arteries and veins were intact and showed no evidence of thrombosis or other obliterative processes. The point of closure

of the enterectomy was intact and not leaking (fig. 1).

Microscopic sections of the jejunum and colon showed the same process of patchy necrotizing arteriolitis with multicentric ischemic necrosis as did the surgical specimen obtained during life. Tiny vessels within the submucosa showed very markedly thickened walls, sometimes hyalanized and sometimes undergoing fibrinoid necrosis; toward the mucosa these became practically necrotic and thrombosed, sometimes with the organization of the thrombi. Just distal to this, there was hemorrhage with characteristic ischemic infarction and necrosis of the underlying mucosa, remarkable chiefly by reason of the focal nature of the lesion. Separating these sharply defined areas of necrosis, the mucosa was reasonably intact. The involvement of the vessels was such that the vessels tended to aggregate in congeries and where the mucosa had sloughed out to expose them there was an area of ulceration filled up with clot (fig. 2).

Case 2. A 37-year-old colored man was admitted with a history of severe headache for 2 days. His blood pressure was 240/160 and the eyegrounds revealed a grade II retinopathy. The urine showed 4+ albumin and a microscopic hematuria. Blood urea nitrogen increased from 64 mg. per 100 cc. to 136 mg. per 100 cc. There was diffuse lower abdominal and periumbilical pain 2 weeks before admission associated with nocturnal nausea and vomiting persisting for 1 week. This pain was present on admission. Temperature was 100°, pulse 110. The stool was positive for occult blood. He expired of uremia 2 months after admission.

FIG. 1. Case 1: gross specimen

Autopsy revealed mucosal hemorrhages of the colon and rectum associated with ulcers as large as 10 cm. in diameter with necrotic bases. These were most numerous in the rectum and sigmoid. The kidneys showed malignant nephrosclerosis and proliferative glomerulonephritis.

Case 3. A 25-year-old Negro man known to have malignant hypertension was admitted complaining of almost constant upper abdominal cramping and pain of 5 weeks' duration. This was unrelieved by food, alkalis or position. The temperature was 99°, pulse 120, the blood pressure 220/160. The abdomen was diffusely tender to deep palpation. The hemoglobin was 5.8 gm. and blood urea nitrogen 60 mg. per 100 cc. Guaiac tests for occult blood in the stool was 4+. Roentgenographic study of the gastrointestinal tract revealed no abnormalities.

There was no response to anti-hypertensive drugs, the abdomen became more tender and rigid and the internist thought that surgery was indicated. No surgery was done because the surgical consultant did not concur in this opinion. The patient expired 11 days after admission.

Autopsy showed uremic enterocolitis of the distal ileum, cecum and ascending colon. The involved areas were multiple, confluent, and greenish black in color. There was malignant arteriolar nephrosclerosis.

Case 4. A 28-year-old Negro man was admitted because of mild joint pains of 1 year's duration. Within the 3 weeks before admission, there was also pain in the shoulders and knees and the appearance of subcutaneous nodules. The pulse rate was 120, the temperature 101°, the blood pressure 160/90. There were no L.E. cells; the blood urea nitrogen increased from 38 to 53 mg. per 100 cc. The creatin clearance was decreased and intravenous pyelogram showed poor renal function. White count was consistently elevated, at times being as high as 43,500 with a leukamoid reaction.

There was an episode of general lower abdominal tenderness and low back pain in the 5th week of hospitalization which recurred in the 6th week, and was accompanied by generalized abdominal cramping which persisted throughout the 7th week. Sigmoidoscopic examination revealed, at the 10-cm. level, a bloody irregular area 1.5 cm. in diameter. During the 8th week, generalized abdominal tenderness and marked rebound tenderness were present. Nasogastric suction was begun for ileus which was present both clinically and on radiological examination. In the 11th week the condition of the patient slowly deteriorated and

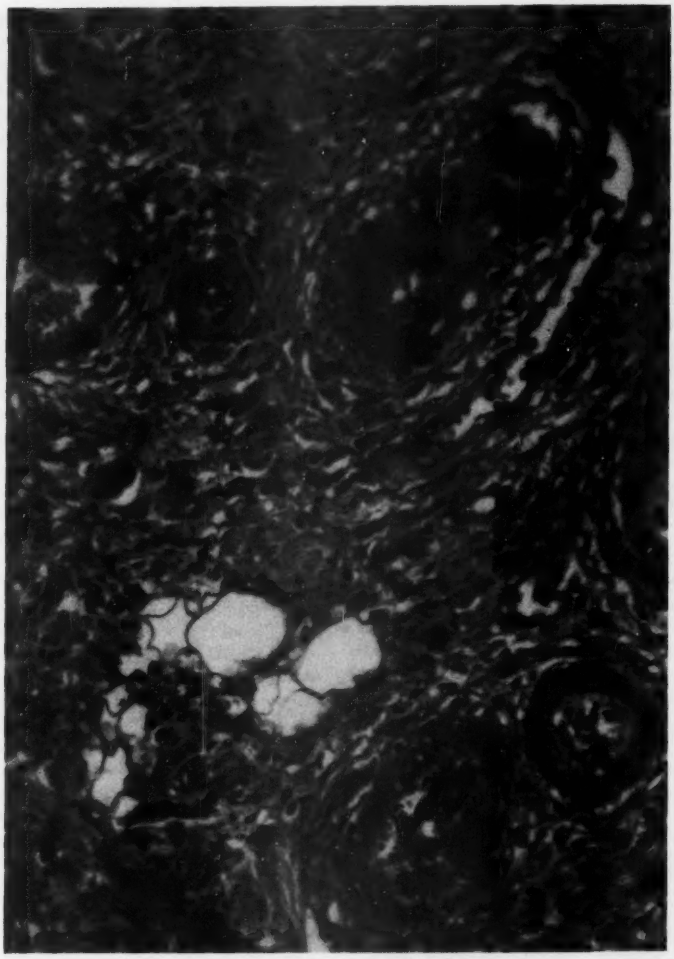

FIG. 2. Case 1: photomicrograph of jejunum

there was a recurrence of abdominal cramping 2 days before his death.

Autopsy showed necrotic areas in the small intestine and colon without perforation. However, there was an extensive peritonitis. Microscopic studies showed periarteritis of the intestinal tract and renal lesions consistent with this disease.

Case 5. A 44-year-old Caucasian man with multiple myeloma was admitted with a weight loss of 35 pounds over a 9-month period. He complained of soreness in the midcervical region, deep aching pains in the legs and shoulders, weakness and fatigue. The blood urea nitrogen was 68 mg. per 100 cc. He was discharged on a maintenance dosage of Meticorten.

He was readmitted giving a history of constipation, nausea and vomiting of 4 days' duration. The temperature was 102° and there was abdominal distention and right lower quadrant tenderness.

The symptoms and signs were those of an acute surgical abdomen and laparotomy was performed. Beginning 6 inches distal to the ligament of Treitz, the jejunum rather abruptly became thickened, swollen and pale, for a length of 30 inches. The arterial and venous blood supply appeared intact. Because of the poor condition of the patient and because there was no evidence of impending gangrene, resection was not performed. He expired the following day of a subauricular heart block.

Autopsy revealed acute hemorrhagic enteritis

with a massive hemorrhage in the jejunum, ileum, cecum, ascending and transverse colon with serpiginous areas of superficial ulceration. Pathologically the lesions were those of uremic enteritis and intestinal para-amyloidosis without specific vascular changes. The kidneys showed florrid myeloma, nephrosis, and extesive tubular damage.

Case 6. A 56-year-old Caucasian man had active tuberculosis for 34 years, and apparently never became sputum negative.

He was admitted because of abdominal distention of 2 weeks' duration associated with vomiting and mild disorientation. The temperature was 100°, the pulse 88, blood pressure 100/60. There was increased guarding of the left lower quadrant, with questionable rebound tenderness. (There was a history of a recent fall and x-ray revealed fracture of VII, VIII, IX left ribs.) Peristalsis was increased, the white blood count was 10,900, 62 per cent of which were polymorphonuclear cells. The hemoglobin was 6.8 and the blood urea nitrogen was 80 mg. per 100 cc., and subsequently increased to 125 mg. per 100 cc. The stool was positive for occult blood.

The abdominal distention increased and x-ray examination revealed several dilated loops of small intestine with air fluid levels. The Miller-Abbott tube did not relieve this distention. A differentional diagnosis between the ileus secondary to uremia, secondary to ruptured spleen, and mechanical obstruction could not be made. On laparotomy, it was found that the liver and spleen were enlarged and that the intestinal dilation was consistent with paralytic ileus. Becoming almost completely anuric, he expired on the 6th hospital day.

Autopsy revealed extensive pulmonary tuberculosis, secondary amyloidosis of the kidney and liver, and a fibrinopurulent inflammation of the ileum and proximal colon which in some areas was so severe as to completely destroy a portion of the wall.

Case 7. A 30-year-old Negro laborer, known to have a 12-year history of hypertension, came to the outpatient clinic complaining of costovertebral angle tenderness, urinary frequency and urgency. He was found to have marked albuminuria, pyuria, and hematuria. In the succeeding 3 weeks, there were progressively severe weakness, diffuse upper chest pain, and periumbilical abdominal pain. In the 4th week, he was admitted to the wards of the hospital. He was thin, lethargic and had a blood pressure of 210/150. There was marked left ventricular hypertrophy, multiple retinal hemorrhages, marked nicking of the retinal vessels, and right upper quadrant abdominal tenderness. The blood urea nitrogen was 163, the white blood count was 11,150 with 84 segmented neutrophils. He was treated by dialysis for constant nausea and vomiting, but despite this he died on the 13th hospital day.

At necropsy, there were many mucosal hemorrhages in the ileum. Microscopically, there was a strikingly acute and chronic inflammatory cell infiltration within the mucosa associated with moderate mucosal sloughing, venous congestion, and nephrosclerosis. Final diagnoses were severe arteriolar nephrosclerosis, and uremia with necrotizing arteriolitis of the ileum.

Case 8. A 33-year-old Negro, with malignant hypertension had progressively severe intermittent right upper quadrant pain over a period of several months, was admitted to the hospital following an episode of massive hematemesis.

The blood pressure was 170/100, there was hypertensive retinopathy, and the heart was enlarged. There was marked voluntary guarding of the right upper quadrant of the abdomen. The stools were guaiac positive.

Abdominal tenderness and pain continued with increasing severity. He died on the 7th hospital day immediately after a convulsive seizure.

At autopsy, the kidneys showed malignant arteriolar nephrosclerous and the gastrointestinal tract showed severe uremic gastritis and moderate enterocolitis.

Case 9. A 54-year-old Negro man complained of weight loss of 35 pounds, constant right upper abdominal and periumbilical pain and progressive weakness of 4 weeks' duration. There was melena 2 days before admission.

On admission to the ward the man was found to be cachectic, dehydrated and moderately jaundiced. His temperature was 102°, pulse 112, respiration 32 and blood pressure 114/82. The liver was tender and 4 to 5 fingers breadth below the costal margin in the right midclavicular line; there was a fluid wave, shifting dullness and generalized rebound tenderness. The hemotocrit was 12 mm., total leukocyte count was 20,600 with 72 per cent neutrophils, 1 eosinophilic granulocyte, 4 basophilic granulocytes, 18 lymphocytes and 1 monocyte. Total serum proteins were 8.6 gm. per cent with an AG ratio of 2.4/6.2. Total serum bilirubin was 4.3 mg. per cent of which 3 mg. per cent was direct reacting. The blood urea nitrogen was 52 mg. per cent, stools were guaiac positive. Cephalin flocculation was 3+, thymol turbidity 9.9 units and prothrombin time was 20.4 seconds compared with a normal of 11.4 seconds. There was x-ray evidence of ileus.

On the 3rd day of hospitalization the patient developed diarrhea. On the 17th hospital day there was an episode of epistaxis; 4 hours later he vomited large quantities of bright red blood. On the

18th hospital day ileus recurred and Levine tube suction was begun. He died that same day.

At necropsy the gastrointestinal tract was filled throughout its length with old blood. There were two small bleeding points in the lesser curvature of the stomach, the result of ulceration of aneurysmal dilation of the arteries of the stomach wall. The mesentery was studded with similar nodular aneurysms many of them at the mesenteric border. Microscopic sections of the gastrointestinal tract as well as those of the heart, kidneys, intestines, liver, striated muscle and prostate showed a widely disseminated necrotizing angitis, morphologically consistent with polyarteritis nodosa.

Case 10. A 31-year-old Negro with essential hypertension had been treated with Reserpine, Digitalis, and Mercuhydrin without response. He was admitted to the ward complaining of intermittent pain in the entire upper abdomen of 1 week's duration. The pain was sudden in onset and relieved somewhat when he lay on his right side.

Blood pressure was 200/135, pulse was 120, and respiration was 28. He was lethargic and there was marked hypertensive retinopathy. The heart showed very marked left ventricular hypertrophy; the liver was enlarged 3 fingers breadth, and was tender. There was bilateral costovertebral angle tenderness and marked albuminuria and microscopic hematuria with hyaline and finely granular casts. The total leukocyte count was 3000, and blood urea nitrogen was 205 mg. per cent.

The patient's clinical condition deteriorated rapidly. On the day before death, the CO_2, chlorides, and sodium remained low in spite of efforts at correction. The potassium was kept within normal range with resins until the day before his death when it increased to 7.1. He had three bouts of epistaxis and bloody stools. Abdominal output decreased to less than 100 cc. per 24 hours, and the blood urea nitrogen rose to 346 mg. per cent.

At autopsy, there was ulcerative uremic enterocolitis without evidence of arteritis. The kidneys showed malignant arteriolar nephrosclerosis.

Case 11. A 50-year-old Negro man with a 4-year history of hypertension was admitted to the surgical ward giving a 10-day history of gastrointestinal bleeding and complaining of right lower quadrant and suprapubic pain. The abdomen was guarded. The fundi showed marked arteriolar narrowing, hemorrhages, and exudates. A pericardial friction rub was present and there was a marked hypertensive myocardiopathy. The blood urea nitrogen was 120 mg. per cent. Hemolytic *Staphylococcus albus* was recovered on urine culture and he was treated with sulfasuccidine, Gelusil, Probanthine, and a bland diet. The initial clinical diagnosis was lower gastrointestinal bleeding due to carcinoma of the colon. He lapsed into coma and died on the 17th hospital day.

At necropsy, there were severe chronic pyelonephritis, and marked uremic gastritis, jejunitis, ileitis, and colitis.

Case 12. A 75-year-old Caucasian man was admitted to the surgical ward with a tentative diagnosis of gastrointestinal tract malignancy. There was a history of approximately 50 pounds in weight loss in the past year, right lower quadrant pain of 5 months' duration, and of constipation and change in stool habits over an undetermined period. A biopsy of the colonic mucosa was reported as showing "vasculitis" and he was transferred to the Medical Service.

The clinical course was marked by increasing lethargy, generalized convulsions and, finally, by hypertension and respiratory failure. Laboratory data showed a blood urea nitrogen of 11 mg. per cent on admission, rising to 184 before death. There was persistent albuminuria, pyuria, and granular and cellular casts.

At necropsy, the gastric and duodenal mucosa was hyperemic with multiple 1- to 3-mm. submucosal nodular areas and many bluish submucosal hemorrhagic areas throughout ranging from 1 to 4 mm. in diameter. Microscopically, sections of the gastrointestinal tract showed marked disseminated arteritis. The kidneys showed lesions of both polyarteritis nodosa and chronic pyelonephritis.

COMMENT

Uremia is a complex clinical syndrome of renal insufficiency and metabolite retention, having no constant anatomical basis. Since it is the end result of a diversity of disease processes affecting metabolism and renal function, it is difficult to clearly distinguish the lesions due to uremia *per se* from those of the primary process. Although uremia affects many organs and tissues of the body, we are concerned here only with those lesions of the gastrointestinal tract.

The process by which alterations in gastrointestinal physiology are produced and the mechanisms of the pathological changes seen at autopsy are not well understood. It has been postulated by Treitz[5] that the changes are the result of chemical or bacterial action on metabolic products excreted into the gastrointestinal tract in uremia. Jaffé and Laing[2] are of the opinion that the ulcerations are secondary to hemorrhage resulting from the hemorrhagic diathesis which is common in uremia. Hlava[1] and Pineau[4] believe

that the initial lesion is a thrombosis of the small blood vessels of the intestinal mucosa. In our own material we have seen lesions which we consider examples of each of these processes but we have been particularly impressed by the frequent occurrence of a necrotizing vasculitis which seems to offer the most logical explanation of the triad of pain, ileus, and melena encountered in our group of patients.

Not satisfactorily explained is the fact that necrotizing arteritis was present in some of the histologic specimens and absent in others. This arteritis is similar to that found in disseminated lupus erythematosus and in polyarteritis nodosa, diseases which frequently have a renal component. A somewhat similar vasculitis of the gastrointestinal tract is seen in other types of sensitivity (food, drug, Henoch's purpura), and also following resection of coarctation of the aorta. In these latter conditions, a primary renal component seems to be lacking.

Of our 12 cases, 6 were young hypertensive Negro men. Other observers have called attention to the high incidence of malignant hypertension in this group of people. This fact, which is well substantiated by clinical observation, may represent an additional etiologic factor which as yet is poorly understood.

In the altered physiologic milieu of uremia due to whatever cause, loss of renal function, metabolic derangements, hypertension, and altered tissue sensitivity are often closely associated and a clear-cut pathogenetic role cannot be assigned to any one of these processes. With our present knowledge, we cannot definitely distinguish between vascular lesions resulting from the metabolic injury of renal insufficiency or from the physical injury of hypertension or from the allergic injury of hypersensitivity. Similar lesions may be caused by each of these factors alone or in combination.

The frequency of gastrointestinal symptoms in uremia is common knowledge but the incidence of acute manifestations is not well documented. On the basis of our own material, we can present no data but in a study of 13 cases, Jaffé and Laing found hemorrhage in 53 per cent, and pseudomembranous and ulcerative changes in 20 per cent.

There seems to be no characteristic pattern of the pain although in many of our patients the pain was continuous, sometimes persisting for days and occasionally showing remissions. Periumbilical and right upper quadrant pain were mentioned frequently. We believe that arteritis is a reasonable explanation for pain but local spasm and peritoneal irritation are possible causes.

Moyer[3] believes that the metabolic ileus seen in uremia has the symptoms and signs of mechanical ileus because the spasticity tends to be local and serves functionally as a mechanical block.

The hemorrhage may be overt and life-threatening or it may be manifested only by the presence of occult blood in the stool. Although this hemorrhage may be the result of the hemorrhagic tendency in uremia, we believe that the more common cause is ulceration. These ulcerations may be shallow, small, clinically silent or they may be extensive, deep and associated with gangrene or perforation.

Symptoms of the acute abdomen in a clinical setting of uremia should suggest gastrointestinal lesions similar to those of the cases reported here. There are no pathognomic features and the problems of differential diagnosis are obvious. Management must be in accord with generally recognized surgical principles.

In summary, 12 cases of uremia having in common gastrointestinal lesions of such a nature as to simulate acute surgical conditions of the abdomen are presented and some aspects of pathogenesis are discussed.

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WOUND HEALING II: CHEMICAL INFLUENCE OF CONTRACTION AND MIGRATION OF REGENERATE*

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INTRODUCTION

Recent investigations on the chemical and morphologic changes which accompany the healing of open wounds in mammalian skin would seem to cast some doubt on the widely held theory that granulation tissue, and more specifically collagen, is the primary element responsible for contraction and ultimate closure of the wound.

Although the earlier work of Abercrombie and associates[1] seems to indicate a close correlation between the increase in collagen content of the wound and the degree of contraction, this correlation was not substantiated by later experiments performed on scorbutic guinea pigs.[2] As a consequence, the authors suggested that fibroblasts in the granulation tissue might be responsible for approximation of the edges of the wound.[2] More recently, Watts and associates[14] combined chemical analysis and mechanical interruption of granulation tissue and reported that, under the conditions of their experiments, excision of central granulation tissue in open skin wounds did not interfere with the rate or extent of contraction. They state, further, that appearance or disappearance of hexosamine, collagen or tyrosine in granulation tissue did not greatly affect the rate or extent of contraction.[15] Their attention was then drawn to a very cellular mass underlying the epithelium of the advancing skin edge which they termed the "picture frame" and to which they attribute the major role in the mechanism of contraction.

The latter work was of particular moment to our group for we had observed the same events in our laboratory.[7] We had excised granulation tissue from open skin wounds and noticed little effect in the reduction of wound size by a process which we felt was analogous to contraction. We observed that disruption of a cellular band of tissue beneath the advancing skin edge delayed contraction but only so long as was required for the cells to regroup, after which the previous rate and extent of contraction recurred.

However, since Dunphy and Udupa[4] had characterized repair sequences chemically by the predominance first of polysaccharides and then of glycoproteins, we felt that selection of chemical agents which would influence this sequence would allow us to study the mechanism of repair without mechanical disruption of the tissue and might offer a clue to the kinetics involved.

METHOD

Eighty male Wistar albino rats weighing between 150 and 200 gm. were individually caged 3 weeks in the environmental conditions of our laboratory, receiving laboratory chow diets and tap water *ad libitum*. For contraction studies, we placed the wound on the right dorsum of each animal during light ether anesthesia, depilating an area 5 cm. square and excising from the center a 2.0-cm. circle of skin extending to but not including underlying fascia. No dressing was applied. On the day of wounding and in each subsequent 24-hour period, representative but randomly selected animals were sacrificed, after weighing, from each of the following groups.

Group 1 (control): 24 animals were observed for *per primum* healing.

Group 2 (uncoupling agent): thyroxine, ergotamine tartrate, gramicidin, and dinitrophenol (DNP) were injected into the cell group at the tissue-tissue interface beneath the wound edge in quantities sufficient to arrest contraction by the end of the 2nd injection day. Although each agent employed arrested the contraction process satisfactorily, DNP was selected as the standard uncoupling agent and 100 mg. per kg. were injected daily per animal. This dosage was toxic to

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the animals, resulting in their deaths between the 5th and 6th postwounding days.

Group 3 (phosphorylating agent): 22 animals received DNP as indicated above, with the addition of adenosine 5-monophosphate (AMP),* 100 mg. per kg., in the cell layer at the wound edge.

Group 4 (counter uncoupling agent): 24 animals were utilized, receiving the same quantities of DNP and AMP as in group 3 but in addition receiving *N*-acetyl D-glucosamine (NADG),† 3.0 gm. per kg., injected into the cell layer at the wound periphery.

Gross analysis of contraction. Following sacrifice, eschars were gently removed and evaluation made of decrease in void. This was carried out by photographing each animal with color film at a fixed focal distance. Similar projection of the completed negative at a fixed distance allowed tracing the wound outline on the day of wounding and at successive daily intervals, such that a series of concentric ellipses were obtained. By tracing these ellipses on graph paper a percentage approximation of decrease in wound void could be obtained.

Microscopic examination of tissue. Representative animals from each group were sacrificed each day postwounding and the entire area of the wound within the area of epilation was excised down to and including the fascia of underlying muscle. This tissue was fixed in position on cork containers to approximate as nearly as possible the excised wound. Following fixation in Zenker-formal solution, sections were cut at 7 microns thickness through the wound void from periphery to periphery. These sections were stained with chrysoidin and counterstained with either hematoxylin and eosin or Foot's modification of Masson's trichrome stain.

Chemical analysis of healing. Hexosamine determinations were carried out according to the method of Boas.[3] Collagen determinations were computed according to the method of Neuman and Logan.[6] Tyrosin determinations were carried out by the method of Udenfriend.[11] Lactic acid determinations were done according to a method developed in our laboratory.[8]

* The *N*-acetyl D-glucosamine utilized in this study was provided by Charles Pfizer and Co., Inc., Brooklyn, N.Y.

† The adenosine 5-monophosphate in this study was supplied as My-B-Den by Ames, Inc., Elkhart, Ind.

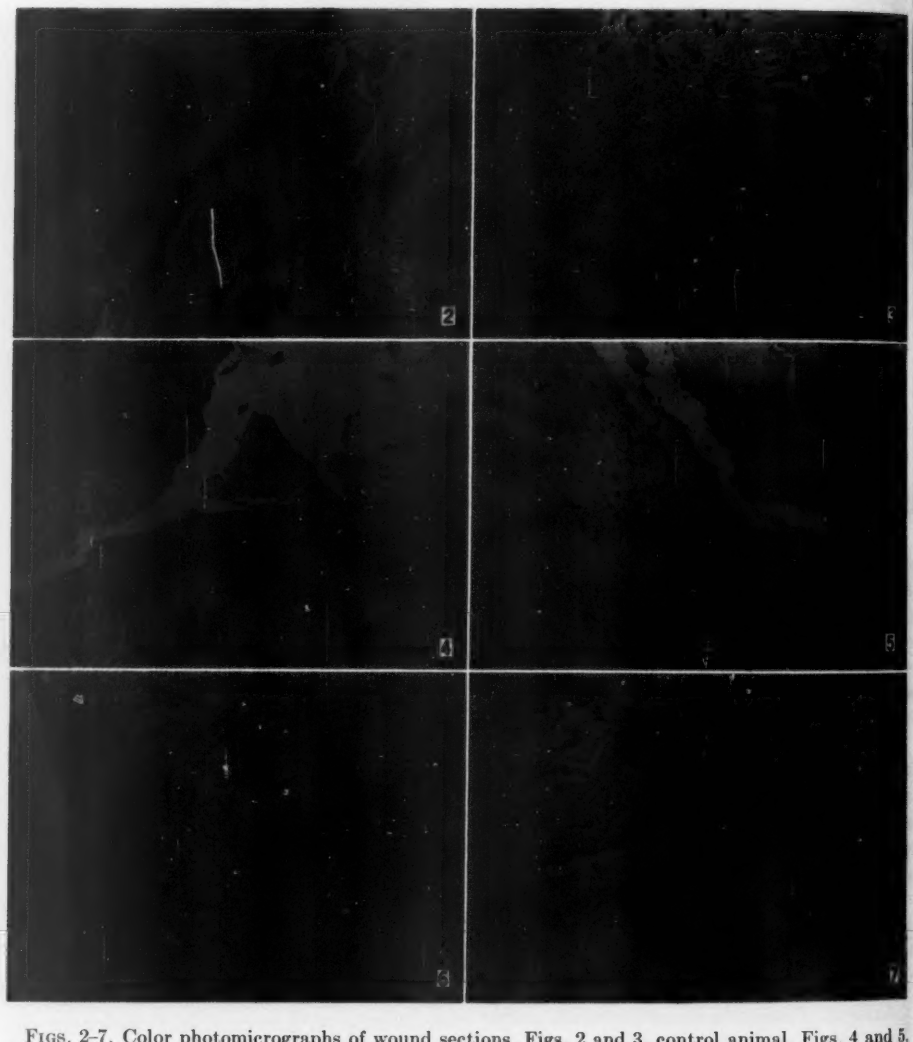
FIG. 1. Position of wound with postwounding ellipse.

RESULTS

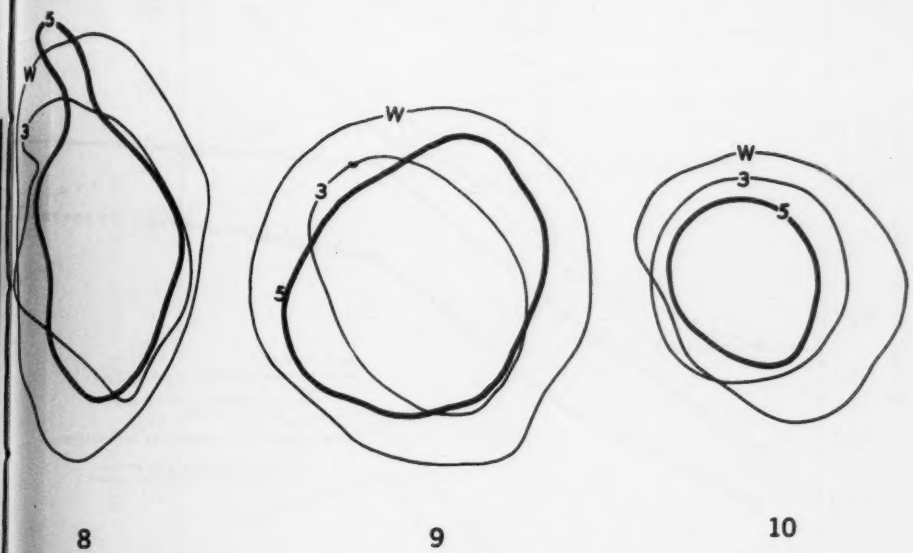
The results are shown in figures 1 through 15. Following operation, wounds in all animals assumed an eliptical configuration although a circular section was excised (fig. 1). This configuration resulted from the differential pull according to the contour of the animal and is essentially the same for all tissue excised in similar positions. Within 3 to 4 hours, serum and fluid had dried to form an eschar. In the control animal, this eschar thickened, became firm, and was detached as early as the 5th or 6th day. By the time the eschar sloughed spontaneously, regenerate was apparent on each face of the ellipse.

By introducing the DNP uncoupling agent at the time of wounding and on successive postwounding days, it was possible to arrest contraction after the 2nd postwounding day. In that interval, migration of the regenerate had begun, as will be noted by examining figures 2 and 3, but it was also arrested after the 2nd postwounding day.

Contraction in void. In control animals, contraction began by the end of 36 hours; by the end of the 4th day, the wound was reduced approximately 30 per cent as indicated in the concentric ellipse technique (figs. 8–10). In those animals treated with DNP alone there was initial retraction such that the wound by the 3rd day appears to be as large as that on the day of wounding. This observation indicates that the size of retraction evident in the first 24 hours produced a void larger than the original operative site. By the 6th day the void was reduced in



FIGS. 2–7. Color photomicrographs of wound sections. Figs. 2 and 3, control animal. Figs. 4 and 5, DNP treated animal. Figs. 6 and 7, DNP treated animal with counter administration of NADG. Figs. 2, 4 and 6, ×50. Figs. 3, 5 and 7, ×100. Chrysoidin with Foot's modification of Masson trichrome stain.



8 9 10

FIGS. 8–10. Outlines of wound area. Fig. 8, control; Fig. 9, DNP treated animal; Fig. 10, DNP treated animal with counter administration of NADG. *W*, day of wounding; *3*, 3 days postwounding; *5*, 5 days postwounding.

size by not more than 15 per cent of its original size. The simple addition of NADG with AMP after DNP treatment resulted in a wound with retraction approaching that of the control and with contraction which had reduced the void area by 30 per cent at the termination of this experiment on the 6th day (figs. 8–10).

Migration of regenerate. Examinations of the tissues from control animals indicate a gradual increase in cellularity in the area immediately underlying the wound as well as in the areas beneath the epithelium at the edges, "the organizer cells." Although leukocytes are present in great numbers, fibroblasts are either attracted to or migrate to the site of the wound in ever increasing numbers as repair progresses. By the 4th day (fig. 2) one can already detect the presence of a few collagen fibers. The deposition of collagen continues so that by the 6th day a well organized stroma has been formed, consisting of blood vessels, bands of collagen fibers and cellular elements.

Although mast cells can be seen along the larger blood vessels in the hypodermis, they are not particularly striking as to size or granularity (fig. 3). In contrast, administration of the uncoupling agent, DNP, seems to arrest both fibroblastic migration and activity (fig. 4). Even as late as the 4th day, the area adjacent to the wound is markedly lacking in collagen fibers (fig. 4). Typically, at this time, the tissue has a bleached out appearance and the cellular layer consists primarily of leukocytes (fig. 5). The administration of NADG and AMP to DNP treated animals not only reverses the effects of the uncoupling agent, but increases both the rate of fibroblastic migration and deposition of collagen (fig. 6). In addition to this, the number of mast cells seems to be markedly increased and their granules are very prominent (fig. 7).

Hexosamine. The addition of the uncoupling agent DNP produced higher hexosamine values as compared to the control animal (fig. 11). From previous work[9] we know that hexosamine levels begin to fall in untreated controls between the 5th and the 7th day, returning to normal by the 8th to the 9th postwounding day. In DNP treated animals there was a steady rise to day 3 with no indication of fall beyond postwounding day 5 or at the conclusion of this experiment. On the other hand, addition of NADG to DNP provided not only higher levels of hexosamine in the first 3½ postwounding days but resulted in a marked fall after the 3rd day to a level below that of the

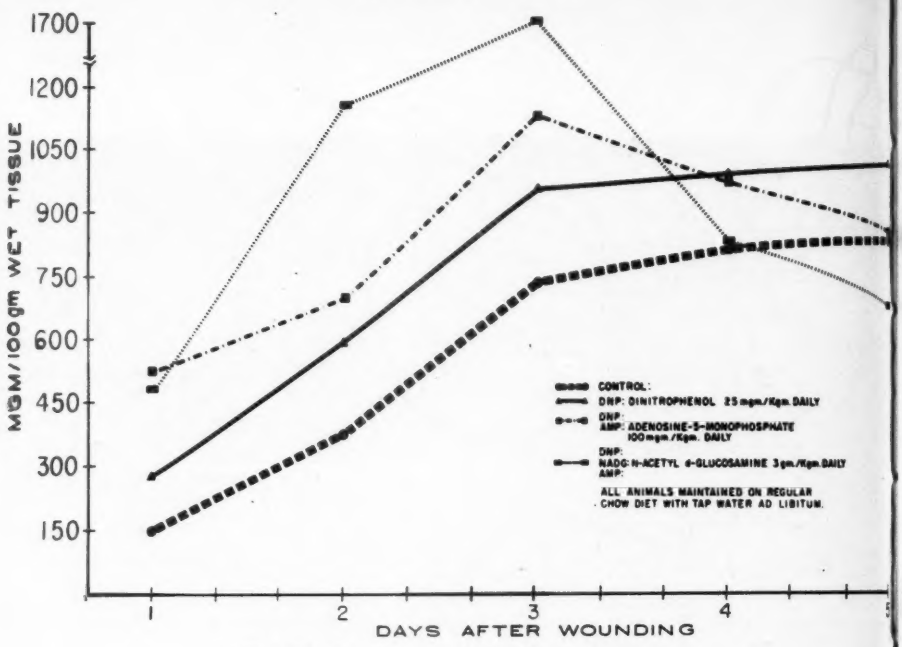


FIG. 11. Hexosamine determinations regenerate

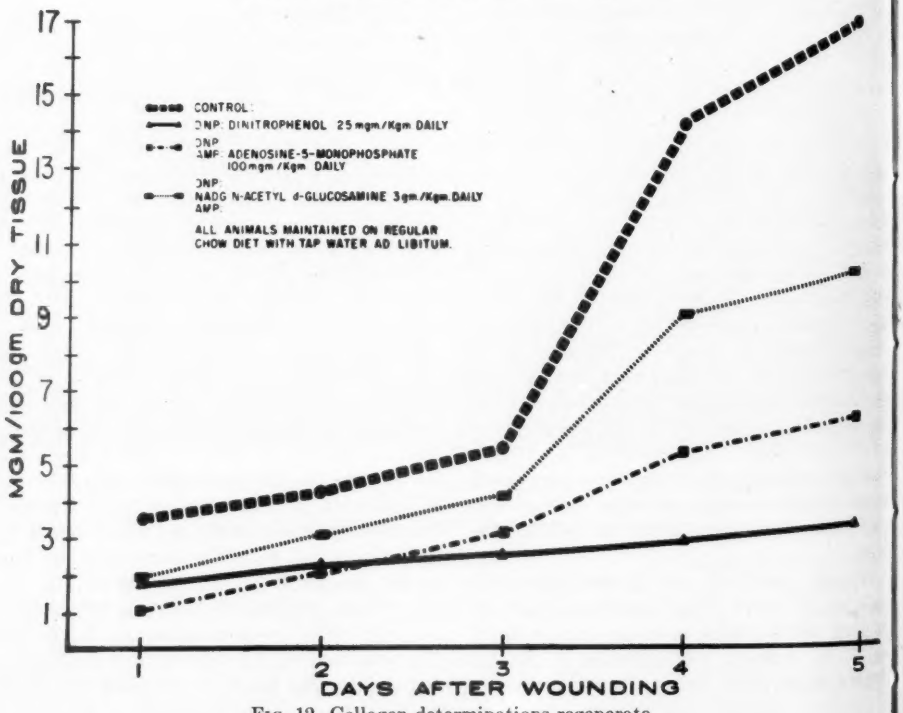


FIG. 12. Collagen determinations regenerate

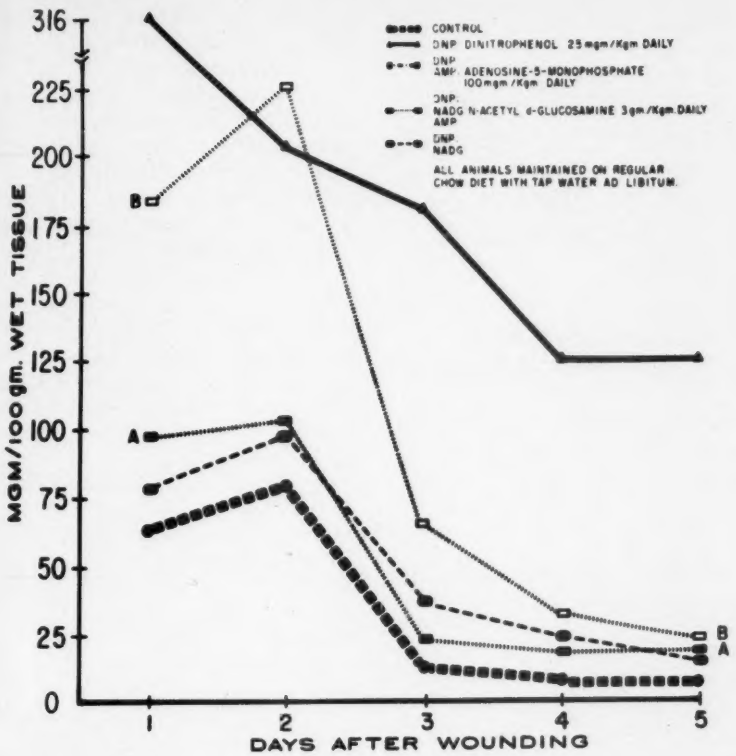


FIG. 13. Lactic acid determinations regenerate

control. The rise in hexosamine concentration could be expected from the direct administration of *N*-acetylated hexosamine, but the fall after the 3rd day is considered extremely significant.

Collagen concentration. In these experiments, the control animals followed a curve noted by us[9] and other investigators[12] (fig. 12). There is an increase in collagen concentrations after the 3rd postwounding day, with a steady rise extending to the 20th and 25th postwounding day, reaching 80 per cent of normal skin values at that time. The DNP group began at lower than control levels and sustained this low value throughout; counteradministration of NADG produced values which reached 60 per cent of control collagen content, confirming the morphologic observation.

Lactic acid. Untreated albino rat skin contains approximately 10 mg. per 100 gm. of tissue wet weight of lactic acid. After wounding, these values for control animals rose to 75 mg. by the 2nd postwounding day, after which they fell to normal levels between the 3rd and 5th day (fig. 13). In DNP treated animals, values in excess of 300 mg. were obtained, falling slowly to approximately one-half this level just before expiration of the animal. Animal groups administered NADG began with levels in excess of 175 mg., rose to a peak and then fell rapidly from 200 mg. to approximately 50 mg. in a 24-hour period. This time interval coincided with the appearance of fibrosis and increased cellularity as illustrated by the fixed sections (fig. 6).

Tyrosine. As an index of noncollagen proteins in normal rat skin, determination of tyrosine varies between 1.5 and 3 gm. per 100 gm. of dry tissue. The fall in tyrosine concentration with increasing time interval and the slow subsequent rise indicate a relative fall in noncollagen protein when collagen content rises in the control animal. In the animals administered the uncoupling agent, tyrosine values fell to a low normal value and stayed at that point. Administration of

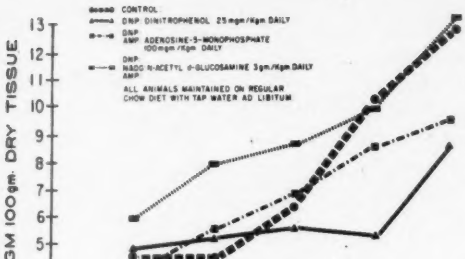


FIG. 14. Tyrosin determinations regenerate

NADG to the uncoupler agent-treated animals provided a general increase in total wound protein which paralleled the rise in collagen after the 3rd postwounding day (fig. 14).

DISCUSSION

Migration of regenerate (granulation) tissue was prevented if contraction were inhibited by excising a cellular layer beneath the wound edge, whereas total excision of migratory regenerate had little effect upon contraction. We were able to arrest activity of the forces of contraction by injecting phosphorylation uncoupling agents beneath the advancing wound edge into that cellular layer which we term "organizer cells." Uncoupling agents produce their effects by causing release of high energy phosphate from compounds which store these phosphates (adenosine 5'-triphosphate, phosphoenol pyruvic acid, phosphocreatine, glyceraldehyde phosphate), and by preventing resynthesis of these compounds. Nonavailable energy is produced (principally heat). Since thyroxine is a halogen phenol, as is DNP, excessive thyroxine presumably produces thyrotoxicosis by uncoupling phosphate energy required for the energy sequences in cells. Mechanical means of inhibiting contraction have been utilized in a classic work by Van den Brenk.[13] After inserting a mechanical device into an excised window of a rabbit's ear, he was able to observe elimination of void by the slow process of migration from a wound whose edges were mechanically prevented from contracting. In this work he applied the classical techniques demonstrated by Medawar and associates,[5, 5a] from which Medawar evolved the hypothesis of rearrangement by migration rather than reduplication in tissue void. Medawar counted mitoses and reported that the tissue mass present could not be explained by dividing cells alone. From the wound edge a migration of regenerate was suggested in which all elements partake, with ultimate apposition of migrating borders. Van den Brenk[13] found that mechanical restriction of contraction simply delayed migration. However, uncoupling the energy processes of "organizer cells" leads to their disruption with resultant arrest of regenerate formation.

Our control studies reveal that the total content of migratory regenerate increased throughout the time of this experiment (6 days). From previous work we have found that such an increase continues for one third of the healing process, but that the content rapidly decreases as the wound becomes smaller. This decrease was called "unexpected," by Watts and associates,[14, 15] but is not necessarily unexpected if one considers that tissue replacement occurs primarily from migration rather than reduplication; as the void decreases in size the amount of total tissue should likewise decrease. We feel this suggestion is compatible with Medawar's hypothesis.

Hexosamine did not fall after the 5th to 7th postwounding day in the animals treated only with the uncoupling agent. In control work in this laboratory,[9] and by others, it was shown that hexosamine values tend to fall to those for normal skin after the first third of the healing cycle. This observation would indicate that hexosamine concentration is not entirely dependent upon serum level or tissue exudates, as suggested by Dunphy and Udupa[4] and Watts and associates,[14, 15] since hexosamine decline should be observed in all groups if cessation of mechanical leakage from coagulation were responsible for hexosamine content. Shetlar and associates[10] have measured uronic acid content as well as hexosamine (suggested by Watts[14, 15] as preferable to hexosamine alone for total polysaccharide accumulation) and note that uronic acid levels rise slowly in the postwounding period of control animals reaching a peak 25 to 30 days postwounding. These investigators suggest that hexosamine identifiable polysaccharides perform distinctly different biologic work as contrasted with uronide containing complexes. We concur; by countertreating our uncoupler administered animal with NADG, hexosamine levels rapidly decline to those of normal skin.

Probably, hexosamine identifiable polysaccharides are utilized in reactive processes of cellular elements in the migratory regenerate at the time when biologic work load is at its peak for those cells. NADG may also provide fuel for energy sequences of the cellular elements of the migratory regenerate. Uronic acid containing complexes seem important in resorption; this problem is the subject of subsequent reports.

When NADG was counteradministered to contraction arrested DNP animals, increase of collagen content and concentration in the regenerate did not appear until contraction recurred. However, once contraction resumed, collagen became quickly apparent (4th day), in morphologic sections, and chemical values indicated that collagen concentration began a rapid rise at this point. In those animal groups wherein regenerate was excised just before closure but in which the wound subsequently closed, tensile strength of the wound was reduced 60 per cent. Collagen deposition seems primarily concerned with development of wound tensile strength.

Tyrosine determinations did indicate a progressive loss of noncollagen protein from our control wounds, with a fixed low value in the uncoupling agent-treated animal. Administration of NADG increases the amount of collagen and of noncollagen protein.

We feel that lactic acid concentrations are significant because they represent the means by which the energy activity of the migrating regenerate can be estimated. Glycolysis and aerobic oxidation sequences as described in the tricarboxylic acid cycle are the bases for recovery activity of a tissue subjected to trauma. A high lactic acid concentration in the uncoupling agent-treated animal is an indication that only a small part of available carbohydrate compounds are passing into the more efficient sequences of aerobic cycles. In the DNP treated animal, lactic acid values in the postwounding period remained elevated and the animal expired. Despite continued administration of an uncoupling agent to the animal, counter treatment with NADG and AMP provided the uncoupled cells with sufficient energy to begin recovery.

SUMMARY AND CONCLUSIONS

1. Forces responsible for contraction are not inhibited with excision of migratory regenerate but the formation of migratory regenerate is inhibited by a chemical modification of the activity of those cell groups which are apparently responsible for contraction.

2. A small group of cells beneath the advancing edge of the wounds resembling fibroblasts (organizer cells) apparently control the rate, quality and quantity of the entire healing process.

3. A sustained high level of hexosamine concentration in the regenerate of dinitrophenol (DNP) treated animals indicates that hexosamine is not predominantly dependent upon serum proteins and tissue exudate for its concentration, and may represent polysaccharide or polysaccharide-protein complexes which are responsible for energy sequences in the cellular elements of the regenerate.

4. The early appearance of collagen in high concentration and total content in DNP administered animals countertreated with *N*-acetyl D-glucosamine (NADG), implicates this acetylated amino sugar in the synthesis of glycoproteins.

5. The apparent increase in the number of mast cells in NADG treated animals would seem to indicate a relationship of these cells in polysaccharide synthetic activity.

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PRIMARY ENDOCARDIAL FIBROELASTOSIS

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Primary endocardial fibroelastosis is a diffuse thickening of the mural endocardium especially of the left ventricle consisting predominantly of fibrous and elastic tissue without associated cardiac malformations or other demonstrable cause. Kelly and Andersen[5] selected cases which showed significant cardiomegaly, marked dilation and endocardial fibrosis of the left ventricle, no major malformations of the heart or great vessels, and no myocarditis or other known cause for the cardiac changes. Also excluded were cases of glycogen disease of the heart, all cases in adults, predominantly right sided lesions, warty vegetations on the valves without evidence of prior stenosis or other valvular lesions and focal necrosis or calcification of the myocardium.

Before the last decade, the diagnosis of endocardial fibroelastosis was rarely made before autopsy. In the past few years, coincident with the surgical management of congenital cardiac anomalies, it has been recognized more often clinically. Endocardial fibroelastosis is an unusual but not rare disease. Kelly and Andersen[5] reported 17 cases in 1956 and collected 79 similar cases from the literature of primary endocardial fibroelastosis using their rather rigid criteria. It may be diagnosed clinically if considered and suspected.

In a period of slightly over 2 years we have encountered 5 cases which fulfill the criteria for primary endocardial fibroelastosis. This is in a community hospital in a city of 20,000 population serving medically an area of approximately 60,000 people. In the same period, 3 cases of congenital hypertrophic pyloric stenosis have been seen in the same hospital.

At necropsy, the heart is greatly enlarged. The chambers, especially the left ventricle, are dilated. The endocardium is diffusely thickened, often being as much as ten times as thick as normal,[9] smooth and yellowish gray to "porcelain-white."[4] On gross examination, the myocardium is usually hypertrophied but otherwise appears normal.[5]

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The epicardium is normal, as is the pericardium.[4] Associated necropsy findings consist of pneumonia, congestive heart failure, tracheobronchitis, and otitis media,[5] atelectasis of the left lower lobe due to compression of the main stem bronchus by the enlarged heart and thrombotic and embolic phenomena.[5]

Microscopically, the most striking feature is the great overgrowth of collagenous and elastic tissue components of the endocardium.[1, 4, 6] The thin walled venous channels in the myocardium are often greatly dilated and distended with blood.[6, 8, 11]

The altered physiology is that of left heart failure with pulmonary edema.[2] The pathogenesis has not been established although numerous theories have been postulated.[3, 6]

Clinically, the main findings are dyspnea, tachycardia, congestive heart failure and infection.[5] Examination also reveals cardiac enlargement, heart sounds of poor quality, either no murmur or a faint one and signs of heart failure, often with rales and enlargement of the liver. The electrocardiogram is not pathognomonic but signs of left ventricular hypertrophy are usually present. There is a normal blood pressure and often a gallop rhythm.

The clinical diagnosis is made on the following: an infant usually between 6 months and 5 years of age, who has been in previous good health, develops failure to gain weight and increasing dyspnea without cyanosis usually attributed to an upper respiratory infection. There is clinical and x-ray evidence of cardiac enlargement with congestive failure. There either is no murmur or only a faint apical systolic murmur. There are a normal blood pressure and normal peripheral pulsations. One must exclude primary disease of the kidney, rheumatic fever and other malformations of the heart. Glycogen storage disease of the heart and cases of anomalous left coronary artery are hard to exclude clinically. Paul and Robbins[7] state that it is not necessary to rule out the latter because it too is improved by the surgery suggested for endocardial fibroelastosis.

The usual treatment is medical for congestive

heart failure and intercurrent infections. Digitalis, oxygen, diuretics and antibiotics are used. Sometimes there is temporary improvement but usually there is eventually a fatal outcome. Although possibly some cases may spontaneously recover, to date, this has not been clinically documented.

During the past 2 years 5 patients have been studied. The first patient is C. H., a white female 16 months of age. The parents refused surgery for this patient. She is alive 6 months after diagnosis but is doing poorly. The second patient, I. H., a colored female 24 months old, never recovered from cardiac failure after entering the hospital. A third patient, R. P., a colored female 23 months old, died of a cerebral embolus while we were attempting to prepare the patient for surgery. This occurred 6 weeks after the onset of congestive heart failure. A fourth patient, R. B., a colored male 20 months old, was prepared for surgery. This patient had a cardiac arrest during the induction of anesthesia. The heart action was restored by cardiac massage and Poudrage was completed. The patient died the 1st postoperative day. A fifth patient, R. M., a colored male 14 months old, had a Poudrage procedure May 11, 1956. He ultimately died December 31, 1957, 19 months later. Postoperatively he was improved, with weight gain, normal development and less symptoms of cardiac failure; however, the size of the heart did not decrease postoperatively, with improvement of clinical symptoms. Paul and Robbins[7] state a similar experience in regard to the size of the heart in the three patients they reported in 1955.

Surgical therapy is based on the altered physiology of ischemia of the myocardium. Thompson and Plachta[10] report that in animal experimentation three reactions to talc in the pericardial sac are found: (1) hyperemia of the myocardium with dilation of pre-existing blood vessels and formation of new vessels in the myocardium; (2) foreign body granuloma involving the pericardium and superficial surface of the myocardium; and (3) adhesive granulomatous pericarditis without constriction, and anastomosis of extracardiac vessels with myocardial vessels through the bridge of granulomatous pericarditis.

Thompson and Plachta[10] and Beck[1a] have used this form of therapy in advanced arteriosclerosis of the coronary artery with prolongation of survival of seriously ill patients.

Paul and Robbins[7] describe a simple operative procedure. An anterior thoracotomy incision is made through the fourth left interspace. The parasternal cartilages are divided above and below to obtain adequate exposure. The pericardial sac is then opened widely anterior to the phrenic nerve and pericardiophrenic vessels. Pericardial fluid, frequently abundant, is completely aspirated and approximately 5 gm. of sterile U.S.P. talc are placed evenly over the surface of the left ventricle, primarily, and to a lesser degree over the anterior surface of the right ventricle. The pericardium is then closed with interrupted silk sutures, care being taken to leave a small opening for drainage of fluid into the pleural space. A thoracotomy tube is placed into the inferior portion of the left pleural space and the chest wall is closed in layers. The procedure is simple and may be performed rapidly and is adaptable to poor surgical risk patients.

In endocardial fibroelastosis the basic difficulty is an interference of drainage from the arterioluminal, arteriosinusoidal, and thebesian vessels into the left ventricle by the thick fibrous endocardium which obstructs these openings.[3, 7, 11] It is speculated that the anastomotic channels provided between the myocardium and extracardiac vessels by the granulomatous pericarditis will provide a site for retrograde drainage of the blood supply of the myocardium of the left ventricle.[7]

In conclusion, although endocardial fibroelastosis is not a common disease, with increased interest in cardiac malformations, the diagnosis can be and is being made more often clinically. This is demonstrated by the five cases presented in this report in a city of 20,000 population in a 2-year period. Because of the uniformly poor prognosis under continued medical therapy, we feel that surgical treatment should be considered in all cases of primary endocardial fibroelastosis.

SUMMARY

1. Five cases of endocardial fibroelastosis seen in a 2-year period are reported.

2. The relative incidence of this disease in a community hospital is stressed.

3. It is felt that surgical management should be considered in all such cases because of the uniformly poor prognosis with medical management.

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SCALENE NODE DISSECTIONS

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INTRODUCTION

In the past 10 years a significant contribution to the management of chest diseases has been the development of scalene node dissection as a diagnostic and prognostic procedure. Very little, however, has been said about the accompanying disadvantages, operative hazards and complications.

The lymph nodes in the subclavian triangle of the neck have connections with the mediastinal and hilar node groups. Pulmonary lesions which spread through lymph channels can frequently be identified by deposits in the scalene nodes. The nodes are also often involved in conditions directly affecting the lymphatics.

The basis for selection of left, right or bilateral dissections has been the lymph drainage from the thorax. The right scalene nodes receive lymph flow from the entire right lung and the left lower lobe. The left scalene nodes receive lymph drainage from the left upper lobe. The lymphatics from the lingula drain to both right and left node groups.

Subdiaphragmatic and esophageal lymph flow also filters through the left scalene nodes. In addition, these lymph nodes receive drainage from the homolateral arm, axilla, chest wall, head and neck. Schiff and Warren[7] recovered a variety of positive scalene nodes from routine autopsies. These included carcinoma of the nasopharynx, thyroid, breast, esophagus, stomach, prostate, uterus and gonads. Other positives were found in cases of histoplasmosis, silicosis, the leukemias, Hodgkin's disease, lymphosarcoma and disseminated tuberculosis.

TERMINOLOGY

Terminology relating to this procedure has been varied and inconsistent. A name for this procedure should describe its anatomical location, the tissue to be excised, and the type of excision done; 11 reports in the literature, since 1951, were reviewed as to title terminology. Two used the term "scalene node biopsy." Two others used the term "prescalene" in their title. "Supraclavicular," "subclavian," "inferior deep cervical," "lower deep jugular," "cervicomediastinal," "deep cervical," "excision" and "exploration" were used once. The term "biopsy" was used 9 times. Identical terminology was found in only 2 reports. It is suggested, since the most widely used anatomical reference is the anterior scalene muscle, that the anatomical part of the standard term be "scalene node." A distinction should be made between biopsy and dissection. Biopsy should refer to the removal of a small portion of a tissue, such as a wedge from a supraclavicular mass, or a single suspected node. Dissection, however, should indicate a clean sweep of regional nodes.

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TECHNICAL CONSIDERATIONS

The operative area in a scalene node dissection overlies the anterior scalene muscle and its fascia, and is bounded on three sides by the internal jugular and subclavian veins and the omohyoid muscle. The dissection is extended further beneath these veins, beneath the innominate vein, and by some advocates, even further into the superior mediastinum, and to the paratracheal nodes. Dissection usually is carried above the border of the omohyoid muscle medially and laterally.

The importance of technique is indicated by Scott's yearly analysis of cases,[8] showing that the positive node yield increased with experience of the operator. The incision extends 6 to 8 cm. laterally from the sternal head of the sternocleidomastoid muscle, and should be slightly oblique above the clavicle. A thorough dissection is done with more facility, if the clavicular head is divided. The posterior belly of the omohyoid muscle, with its fascia, is retracted anteriorly to expose the tissues to be removed. Care is taken to avoid lymphatic leaks on both sides. If the thoracic duct is opened or divided, both ends are ligated. This applies also to other large jugular

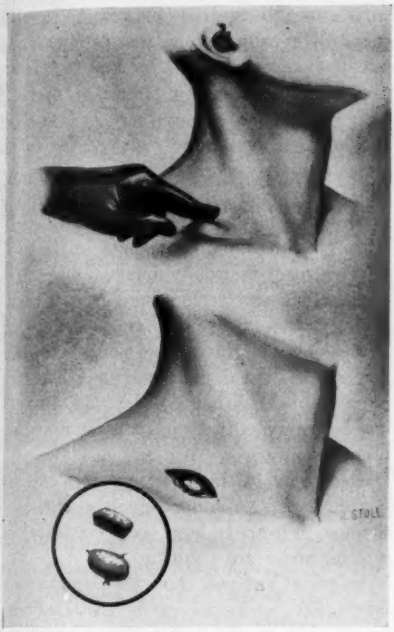

FIG. 1. Scalene node biopsy

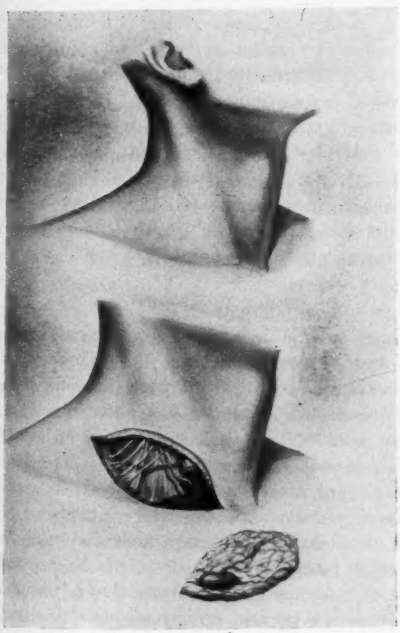

FIG. 2. Scalene node dissection

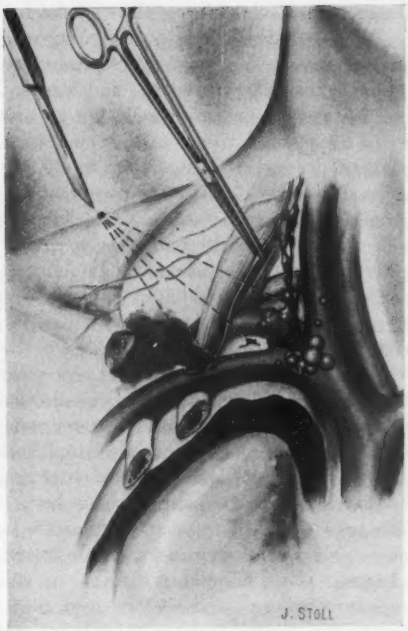

FIG. 3. Operative hazards in scalene node dissection.

and subclavian lymph trunks which may be found on both sides. The tissue removed includes the node bearing areas beneath the internal jugular, subclavian, and innominate veins. The transverse scapular artery and vein are usually taken to facilitate the removal of nearby nodes. Frequently, the operation is directed at removal of a pad of fatty tissue in the subclavian triangle without disturbing the major veins and lymph trunks. This fat pad will contain very few or no lymph nodes, and although it is incidentally removed in the adequate dissection, it is not the primary object of excision. Most of the lymph nodes will lie on the periphery of the prescalene fat pad, since they are located in intimate contact with the major veins. It is this area beneath the internal jugular, subclavian, and innominate veins which should be included in the dissection. An adequate dissection should contain lymph nodes.

INDICATIONS AND ESTABLISHED VALUES

A scalene node biopsy or dissection supplements other established diagnostic methods. Before a dissection is done it should be clear that

all other procedures to be employed have been done. These include multiple sputum cultures and cytological smears, bronchoscopy, esophagoscopy, occasionally nasopharyngoscopy, and x-rays. A search for another primary should not be overlooked. Frequently these priority procedures have been overlooked, where they would have made scalene node dissection unnecessary. Carcinoma of the colon metastatic to the lung was found on one occasion by barium enema after a negative scalene node dissection. In numerous instances a bronchoscopic biopsy gave the diagnosis after a scalene node dissection had been done.[1]

This procedure should be done when necessary as a diagnostic aid in pulmonary, mediastinal, subdiaphragmatic, or systemic diseases, where information on the condition of these lymph nodes would be helpful. It should be used after more conservative diagnostic methods have been inadequate. It should be used when Boeck's sarcoidosis is suspected, whenever there are enlarged mediastinal nodes of unknown cause, or when lymphosarcoma or related diseases are suspected. In pulmonary cancer, the procedure is indicated both as a diagnostic and as a prognostic method, and as an aid to surgical judgment. There are differing views as to whether all cases of bronchogenic carcinoma should have scalene node dissection. It may be used for identification of foreign body substances, such as pneumoconiosis or silicosis. It is of value in determining operability of patients with bronchial carcinoma, although positive findings may not necessarily indicate absolute inoperability.

Diseases with a low yield of positive scalene nodes are carcinoma of the esophagus, mediastinal tumor, pulmonary tuberculosis, diffuse pulmonary infiltrative disease, and squamous cell bronchogenic carcinoma. Scalene node dissection is indicated in these diseases, however, when other diagnostic means are not productive.

Routine autopsy node dissections[9] have upheld the theory of predominantly left scalene node metastases from lesions below the diaphragm. Scalene node dissection may for this reason be of occasional use in the management of subdiaphragmatic diseases.

CONTRAINDICATIONS AND DISADVANTAGES

Scalene node dissection is not indicated for patients with a known diagnosis where it would not influence therapeutic judgment. In those cases with clinically obvious masses in this area, a node dissection should not be done but, rather, a biopsy, limited to the abnormal tissue. A possibly malignant node anywhere, and especially in the neck, is preferably reserved for *en bloc* excision with its primary when possible, and should be removed for diagnosis only after all other efforts at diagnosis have been exhausted.

There are some failures inherent in the procedure. Treatment is usually delayed, due to elective scheduling and performing of the operation and to the postoperative recovery period; 10 days or 2 weeks may be squandered while hospitalization continues, the disease progresses and treatment is withheld. When possible, the dissection should be combined with other procedures, such as bronchoscopy.

Thoracotomy, without previous scalene node dissection for known bronchogenic squamous cell carcinoma, appears to have some statistical support if no nodes are palpable.

Some recent analyses show that squamous cell (epidermoid) carcinoma rarely metastasizes to the scalene lymph nodes.[1, 9] In one series of 33 pulmonary cancer cases having node dissections,[1] 19 were squamous cell carcinoma, none of which gave positive scalene nodes. Undifferentiated (anaplastic) carcinoma and adenocarcinoma, however, metastasized quite frequently; 6 of 9 cases of anaplastic cancer, and 1 of 2 adenocarcinomas, gave positive scalene nodes. Up to 90 per cent of dissections without palpable nodes will be negative, and if there is a definite tissue diagnosis of squamous cell bronchogenic carcinoma, the incidence of positive nodes will be even smaller.

CHOICE OF ANESTHESIA

Local anesthesia has been the preferred method for most of these dissections. This is best decided on an individual basis, however. It is seldom that a patient will permit bilateral dissection at one time with local anesthesia, especially if he is an older patient with arthritis of the spine, has a dorsal kyphosis, or is dyspneic. Others may have extreme anxiety or be otherwise unable to cooperate. A safer, more thorough node dissection and a more informative detailed bronchoscopy are accomplished under general anesthesia. Bronchoscopy with bilateral scalene node dissection under general anesthesia is a useful combination.

DISPOSITION OF SPECIMEN

The importance of complete examination of the specimen cannot be overemphasized. It is unfortunate for a patient to endure the discomfort, risk and inconvenience of operation, only to have the specimen lost, contaminated, or incompletely studied. Evaluation of the specimen begins before operation with thorough palpatory examination. This is extended by finger palpation through the incision at operation. This may reveal nodes otherwise undiscovered along the carotic sheath or behind the subclavian vein. After removal of the specimen it is carefully examined and cut by the surgeon at the operating table. The portion most likely to yield positive findings is divided under sterile conditions and placed in sterile containers. Separate portions are sent to bacteriology and histology laboratories, fully labeled. It is preferred that the surgeon deliver these in person and discuss the nature of the case with the pathologist and bacteriologist. Cultures for tuberculosis, fungi and routine bacterial cultures are obtained on all specimens which are undiagnosed. Preoperative discussions, with other physicians participating in the care of the patient, will supply valuable suggestions. All clinical data, operative information, and laboratory findings are carefully recorded on the patient's chart.

HAZARDS AND COMPLICATIONS

More emphasis must be placed on this procedure as a dangerous operation, rather than on its theoretical simplicity.

Hazards and complications begin with the skin incision. The lateral corner of the usual incision is crossed by the lateral cutaneous nerve, which can be avoided without loss of sensation below the incision. As the dissection progresses, exposing the posterior belly of the omohyoid muscle, its blood supply and innervation may be seen in a delicate web of supporting tissue; and these should be preserved by retracting the omohyoid and its attached fascia anteriorly and downward with a blunt retractor. The phrenic nerve and brachial plexus are best protected by starting the dissection medially beneath the internal jugular vein, carrying the specimen always laterally over the scalene fascia, keeping the phrenic nerve always in view. If this fascia is left intact, a good specimen may be obtained and yet the phrenic nerve and brachial plexus are protected. One phrenic nerve crush occurred[1] when the specimen was reflected medially and the phrenic nerve mistaken for a blood vessel. The patient experienced sudden severe tingling pain in the chest and shoulder.

Air embolism occurs more often than is recognized. It may occur with an opening in even the smallest tributary of the internal jugular or subclavian vein. If the operation is performed with the head of the table slightly elevated, these bubbles collect in the internal jugular vein or more frequently at the junction with the innominate and can be seen through the vein wall early, before a large embolism has occurred. The air bubbles may easily be aspirated with a syringe and fine needle.

Hemorrhage is a constant danger, since this operation is done among major arteries and veins. The most frequent serious hemorrhage is caused by a tear in the subclavian vein. This is produced by a sharp instrument such as a Gelpi retractor or by tearing at the crotch of a tributary vein during spreading action with dissecting scissors. Such an injury in an internal jugular or anterior jugular vein is easily handled, since exposure is adequate. Injury to the subclavian vein, however, may be serious, since it is recessed beneath the clavicle. If a large rent occurs, the clavicle should be promptly resected for exposure.

Any lymphatic trunk, if opened and not ligated may produce a chylous fistula. This is remedied by a drain and pressure dressing.

The vagus nerve is large, lies behind the carotid artery, and is no source of difficulty if kept in mind. The recurrent laryngeal nerve likewise is outside the usual area of dissection, but may be injured in a search for paratracheal nodes.

Pneumothorax is sometimes produced by a tear in the apical pleura in the space beneath the subclavian vein, medial to the anterior scalene muscle. Closure of the incision without drainage, and thoracentesis, will remedy such a complication.

OPERATIVE TIME FOR SCALENE NODE DISSECTION

It is almost the rule for reports to minimize the time required for these operations, the discomfort to the patient under local anesthesia, and the complications encountered. An analysis was made of cases from which the data could be secured. All 12 cases were uncomplicated, were performed by experienced surgeons, were unilateral dissections, and were adequate in extent; all

were performed with local anesthesia. Of the 12 operations, the shortest duration was 17 minutes. The longest operative time was 1 hour and 55 minutes. The average duration was 1 hour and 13 minutes.[1]

DISCUSSION

It is helpful for surgeons undertaking the responsibility of these dissections to reappraise critically the adequacy of the procedure, its shortcomings, and the many responsibilities which must be discharged in order to obtain the best results.

Inadequate dissections are due primarily to the fact that this procedure is considered a simple operation without complications. The earlier accounts describe a small incision, no complications, and only 15 to 20 minutes of operating time. Such a dissection is completely unsatisfactory according to present standards, which require a 5- to 6-cm. incision and over an hour of operating time by an experienced surgeon.

The demand for increasing percentages of positive nodes continues. Extending the dissection increases the number of positives. However, this can be carried to the point where a scalene node dissection becomes more of an operation than diagnostic thoracotomy.

A proper perspective of this procedure in relation to other diagnostic methods must be maintained. Scalene node dissection is the most hazardous, most extensive, most time consuming, and least revealing of diagnostic methods available, short of thoracotomy. It should be the last procedure to be employed before thoracotomy in unknown intrathoracic disease.

SUMMARY

Scalene node dissection has become a useful and fairly well standardized method in the diagnosis and management of thoracic diseases. Surgeons undertaking these procedures are reminded, however, of the many shortcomings encountered, and of the many responsibilities which must be discharged to give maximal value to the dissections.

This is a hazardous, extensive, time consuming, and only slightly revealing procedure. All other diagnostic methods short of thoracotomy should be used before scalene node dissection. Complications may include injury of major or minor nerves, hemorrhage, lymphatic fistula, pneumothorax, air embolism and infection. The operative time averages 1¼ hours. Delay in treatment results unless the dissection is combined with bronchoscopy or other diagnostic methods. Complete examination of the specimen is of great importance.

These nodes are seldom positive with a known primary diagnosis of bronchogenic squamous cell carcinoma. If no nodes are palpable, only 8 to 10 per cent of all dissections will have positive nodes. A distinction is made between scalene node dissection and biopsy.

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DISABILITY EVALUATION

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The evaluation of a patient's disability has been recognized universally as a confusing and complex problem. It involves not only a comprehensive and thorough knowledge of anatomy and physiology, but psychology and human behavior, which are factors that are hard to express in exact terms. In this discussion I wish to point out that the term "disability" refers to permanent disability or loss of function or earning power of the individual. In other words, the functional end result. Also, the patients I refer to in this paper are disabled because of accidental injuries, "arising out of, and in the course of, their employment." Occupational disability is not considered compensable in our state and is not included in this discussion.

Sometimes there is pre-existing disease (such as arthritis) and the injury aggravates this condition, and/or the convalescence is unduly prolonged by the disease. The question arises: how much is due to the injury and how much is due to the pre-existing disease? All of these factors must be taken into consideration when a disability rating is made.

Frequently, a physician is called upon to rate or give the exact percentage of functional loss or disability of a patient. To arrive at a fair and logical conclusion involves a great deal of thought and consideration of the individual patient, his working conditions, and what is expected of the employee. A wide experience in the treatment of injured workers from the time of the injury through the course of their disablement, until they are ready to return to work, is invaluable in estimating whether any permanent disability or loss of function exists. The doctor often has to function as an umpire or mediator between the injured employee and the insurance company, and the employer. The physician must differentiate the often abstract, intangible complaint of the patient and the concrete, tangible signs of disability, temporary or permanent, that may exist.

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It is natural for the injured employee to hope and try to obtain as much monetary compensation for his accident as possible, whereas the insurance company, of course, desires to make a reasonable settlement of the claim. Many employees, I believe, have the erroneous impression that insurance carriers try to pay as little as possible, but I am sure the good, larger companies expect to pay as just and as reasonable an amount as presented by the facts in the claim.

I should like to give a simple example of how I would arrive at a figure or percentage of disability of a certain case. Suppose the patient sustained a severe fracture of the os calcis and had reached the acme of recovery, and is to be rated. I think it is well to consider the disability to as small a portion of the body as possible at first, *i.e.*, the foot; and let us say it is 50 per cent to the foot. If the percentage is to be considered to the leg (lower extremity), the disability would then be about 25 per cent and if the rating is to be to the body as a whole, 10 to 12 per cent. The various compensation boards have set up certain figures for the body as a whole, and the different members of the body.

In my opinion, there should be more uniform compensation laws, probably a national standard of rating and disability awards. Of course, amputations represent a specific loss in most states, and are not usually a source of contraversy, and offer no problem in disability evaluation.

There are two valuable books on the subject of disability evaluation, that I would recommend: *Disability Evaluation*, by Dr. Earl McBride; and *Accidental Injuries*, by Dr. Herman H. Kessler.

The *Journal of the American Medical Association* published an interesting and valuable booklet on February 15, 1958: *A Guide to the Evaluation of Permanent Impairment of the Extremities and Back*, in which great stress is put upon the difference between permanent disability and permanent impairment. It states: "Evaluation (Rating) of permanent disability is an administrative, not medical, responsibility and function." I do not think that such a definite line can be drawn between permanent disability and permanent

impairment, and from my experience, I feel the physician must evaluate the patient as a whole and estimate his loss of function or earning power, to determine the monetary award for the injury. This booklet is valuable to the beginner and affords some idea as to the percentage of functional impairment, but every case must be individualized, and deserves the careful consideration of all the factors involved in the loss of earning power, whether temporary or permanent.

HISTORY

It is most important in examining a patient, to obtain a complete history, including all the pertinent facts of the case, before meeting the patient. This includes age, marital status, previous health and previous accidents, length of time employed by the present employer, wage-work status, and how the employer rates the employee's work.

It is interesting to note how cooperative and anxious to return to work, are patients who are highly paid for their work. Usually, they are good employees with ambition; exaggeration and malingering are not problems in these cases. On the other hand, employees that are constantly shifting jobs and are not well satisfied with their work and pay at the time of the accident, will very often try to stay on compensation and exaggerate their symptoms. Also, if an employee is laid off during the time he is temporarily disabled, often from a minor accident, it is very difficult to rehabilitate him or make a reasonable settlement with him. In many cases, if the employers would allow an injured employee to return to work gradually, at first at light work, then regular work, the problem of rehabilitation and settlement of a disability claim would be much simpler.

MALINGERING

This is a term I avoid using in making a report of an examination of a patient, as it implies an untruth, either in the history, or in the complaint of the patient.

Inconsistencies in the history or complaints should be carefully noted, since they are very apt to occur during the examination of a patient who is willfully trying to deceive the examiner.

EXAMINATION

The patient should be given complete, unbiased physical and, usually, x-ray examinations. His complaints and subjective symptoms should be noted and those portions of the body examined. His clothing should be removed and he should be examined both standing and lying down. His gait and movements should be carefully noted. The objective signs are those that the examiner can see or feel, such as muscle spasm, deformity, or limitation of motion of joints. It is important to note whether the limitation is voluntary or involuntary. A good x-ray examination should be made and any abnormalities noted, whether due to congenital deformities, injury or disease.

I believe that the treating surgeon should take the patient into his confidence when a serious accident has occurred and explain to him the type of injury he has, and give him some idea as to how long he may be disabled. I do think the doctor should make a conservative estimate and be optimistic in his discussion with the injured employee, since, in many cases, it will require 6 months for recovery to take place, and possibly longer before a reasonable estimate can be made as to how much, if any, permanent disability the employee will have as a result of the injury he sustained. In general, it may be well to explain something of the compensation law to the patient, but if he desires details I would refer him to the insurance company or employer.

I believe that the patient should be treated like you yourself would want to be treated under the circumstances. It is important for the treating physician to control the case during active treatment, rehabilitation and restoration of the patient to his former job. In some cases it is well to consult a qualified specialist, such as a neurosurgeon, who understands the treatment and handling of compensation cases.

If the patient employs an attorney while under treatment, I do not think this should change your attitude or method of treatment nor make any difference in the estimation of permanent disability, if any, when a final rating is made. Much too often, an employee will hire an attorney while he is receiving the best of medical care and everything possible is being done by the employer and the insurance company to relieve him and restore him to normal health.

Sometimes, the "Company Doctor" will be inclined to give a low disability rating to the patient, I presume, to make a good impression upon the insurance company and the employer.

In many cases, permanent disability can be

lessened by a judicious, properly carried out, rehabilitation program. One of the largest compensation insurance companies in the United States, the Liberty Mutual Insurance Company, Boston, Massachusetts, regards rehabilitation as being so important, they have established a large, well equipped and well staffed rehabilitation center in Boston, and another center in Chicago, Ill. They make every effort to restore the injured employee to normal health, and if this is impossible, to rehabilitate him and equip him to do some type of work, that he may again be an independent, useful citizen. Mr. W. Scott Allen, of that company has written a very interesting and enlightening book entitled *Rehabilitation—A Community Challenge*. This company feels that the mental and physical restoration of the individual is much more important than a monetary award for his injury.

SUMMARY

There are five cardinal rules in estimating permanent disability that I should like to emphasize: (1) an unbiased attitude on the part of the examiner; (2) a complete history, including the time and the place of the accident and the work status of the patient, as well as other things noted previously in this category; (3) a careful and thorough physical examination, including adequate x-rays; (4) consideration of the age of the patient, the type of work and the severity or extent of the injury he sustained; and (5) always remember that any statement you make should be carefully worded, since it will be used, *verbatim* when the case comes before the Compensation Commission or Compensation Board.

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THE SURGICAL TREATMENT OF CORONARY ARTERY DISEASE*

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Surgery for coronary artery disease has interested some workers for a long time, and there have been many enthusiastic investigators in recent years. Nevertheless, the medical and surgical professions as a whole have not generally accepted any of these operations for widespread application to patients. The purpose of this communication is to attempt to evaluate the status of the operations currently being performed and then to consider certain physiologic observations which are basic to the problem, and to formulate an hypothesis which if valid may well outline a more rational and perhaps more successful attack on the disease.

The first type of procedure has as its primary objective redistribution of blood within the coronary arterial tree. Of these, the Beck I[6] is probably the best studied. It consists of abrasion of the surface of the heart, partial ligation of the coronary sinus, placement of asbestos between the heart and pericardium, and suture of a pad of mediastinal fat to the heart. Introduction of talc into the pericardial sac was described by Thompson and Raisbeck[35] and application of phenol to the surface of the heart has been performed by Harken.[17] After these procedures, it has been possible to demonstrate anatomically increased arterial communications between branches of adjacent major coronary arteries, both in the dog and in the human being, and there is evidence that they provide some protection against early death after experimental ligation of the anterior descending coronary artery of the dog.[10]

Beck and co-workers[5] believe that a significant number of human patients die a "mechanism-death," which consists of ventricular fibrillation triggered by a small area of severely ischemic myocardium. They believe that the intercoronary arterial channels which form in response to the artificial stimulation of the operation can permit a more even distribution of blood throughout the myocardium and thereby reduce the likelihood of this mechanism type of death in human beings. The Beck I operation can be performed with a low surgical mortality, and its advocates present statistics which they interpret as showing a longer survival that would be expected, on the basis of comparative control series. This interpretation has been seriously questioned.[18] Although many surgeons have performed this or a similar type of operation on some patients, relatively few are adequately convinced of its value to perform it regularly or on a large number of patients.

Another potential benefit from an operation designed to increase the intercoronary collateral circulation is relief from anginal pain. Some patients have obtained complete or partial symptomatic relief, often with an increase in exercise tolerance in virtually all of the series reported after operations of this type. However, essentially the same relief, at least for a temporary period, has been obtained after ligation of the internal mammary artery.[2, 14] There are theoretical pathways through which collateral arterial channels might develop from the internal mammary to the coronary artery after increase of the side pressure in the former caused by distal ligation[14] but the experimental evidence is that these do not develop to any significant degree.[2, 15, 30] Furthermore, small groups of patients who received only incision and dissection of the mammary arteries without actual ligation of the vessel have obtained approximately the same results as those who received the ligation.[9] The inescapable conclusion is that the clinical improvement often seen after this operation is due to psychologic factors and the procedure may be considered a form of surgical psychotherapy.

One might logically summarize by saying that operations performed to stimulate the formation of the intercoronary collateral arterial channels might decrease the chances of premature sudden

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death of the patient from ventricular fibrillation. Furthermore, anginal pain is sometimes relieved, but until there is more definite evidence that the more extensive procedures give convincingly better results, the internal mammary arterial ligation must be considered the simplest and safest operation when only this symptomatic effect is desired.

The second major type of surgical procedure for coronary arterial disease has as its objective the actual transport of more blood to the myocardium, from an extra cardiac source. One approach is the removal or bypass of obstruction in major coronary arteries. This work is largely based on studies by Schlesinger and Zoll,[31] and more recently, Szilagyi and associates[33] who point out that nearly all patients with angina pectoris have anatomically demonstrable narrowing of a major coronary artery, and this obstruction is often located relatively proximally, with patent vessels in the distal tree. May and Bailey[24] and Longmire and associates[22] have successfully performed endarterectomy of the main, right and anterior descending branches of the left coronary artery in human beings. Although this represents brilliant technical achievement and some patients have been clinically improved, general acceptance of the procedure awaits proof that the arteries remain open. Certainly, results of endarterectomy in vessels smaller than the popliteal artery have been disappointing in the leg, but perhaps other factors could permit better results with the coronary arteries.

Furthermore, sound application of this technique on a widespread basis probably awaits development of a satisfactory method for coronary arteriography, in order to select accurately the patients who have proximal obliteration of a major coronary artery but have satisfactory outflow tracts distally.

A procedure which has been proposed experimentally and which should be possible whenever endarterectomy can be done and probably is less vulnerable to thrombosis, is the direct anastomosis of an internal mammary artery to a coronary artery distal to an occlusion.[1, 8, 25, 26, 34] This technique theoretically offers some promise, but its rightful place in our armamentarium must await further observation.

Openings have been made between the left ventricular cavity and the central area of the myocardial wall.[15, 23] These procedures have afforded some protection against ligation of the anterior descending artery, but again this is probably the result of nonspecific irritation of the heart wall. It is hard to imagine that the pressure in the ventricular cavity can be very much higher than that deep in the ventricular wall at any point during the cardiac cycle.

Another approach to the problem of providing additional arterial blood from an extracardiac source is the application of a pedicle to the myocardium. The long list of tissues which have been used in the past includes pectoral muscles,[3] omentum,[28] skin and subcutaneous tissue,[38] jejunal wall,[4, 20] lungs,[7, 13, 21] and anastomosis or a graft between the aorta and the coronary sinus for a retrograde profusion of the myocardium through the coronary venous system.[6] These operations are followed by a variable amount of protection against death from subsequent ligation of the anterior descending artery in the dog and the results roughly parallel those aimed at production of intercoronary collateral vessels. The effect in both groups is probably the result of non-specific irritation of the surface of the heart.

There is no very strong evidence that any of the pedicles mentioned above actually increase the quantity of arterial blood available to the myocardium, and where careful studies have been done, the blood in the pedicle was demonstrated not to move toward the coronary arteries.[35]

An exception to this generalization concerning pedicles is the work first described by Vineberg and Walker[37] and variations using the carotid[27] or subclavian.[12] Vineberg dissects the internal mammary artery free and divides it distally. The proximal end is implanted in a tunnel made in the left ventricular myocardium. Corrosion casts, pressure measurements, and observation of the heart after clamping of either the coronary or the transplanted mammary artery offer definite evidence that some blood does enter the coronary circulation through this transplant in some of his animals.[11, 36, 37] The operation has been applied to patients with some success and appears to be gaining favor, but again there has not yet been widespread acceptance by the medical profession.

Now that we have reviewed the general status of surgery in the treatment of coronary arterial disease today, let us backtrack and consider the physiologic principles which are basic to the problem. Although there are anatomical differences, there is no logical reason for believing that

the basic principles governing formation of collateral arterial channels in the heart are different from those in the legs. The general subject of collateral circulation has been well reviewed by Holman,[19] Quiring[29] and more recently by Winblad and associates.[39]

Let us consider a few of the countless situations in which collateral arteries develop. If the femoral artery is occluded acutely, channels already present open very rapidly. If enough blood flow is available to prevent destruction of tissue, more collateral channels develop later. A gradual occlusion permits the occurrence of these processes simultaneously. Many channels also develop if the pressure in a distal arterial tree is lowered by an arteriovenous fistula placed proximally. If an inflammatory carcinoma of the breast drains increased quantities of blood from the existing sources of supply with inevitable lowering of pressure at the point of delivery, more and larger vessels develop and carry more blood to the region.

A common denominator seems to be present in these and other situations where collateral arterial channels develop, and conversely these vessels seem to develop consistently where this common denominator is present. The two components of this common denominator are the presence of two arterial beds with a difference in the pressure in each, and some sort of small vascular communication between them. If this theory is correct, one might hypothesize that collateral channels will develop if a pedicle is capable of carrying large quantities of arterial blood under high pressure to a point very near a hypotensive coronary artery, and if capillary connections exist between the two.

It is interesting to consider some of the work which has been done in the past from the point of view of this hypothesis. The first requirement stated above is that there must be a difference of the pressure in the two arterial beds. Have the arteries in the pedicles described in the past been able to maintain a higher pressure at the point of contact with the heart than that in the coronary arteries? We know that the volume of blood which is deliverable from a cylindrical conduit in a given time varies as the fourth power of its diameter so that halving the diameter decreases the blood carrying capacity by 16 times. For a given flow the pressure drop across a given conduit varies as the square of its diameter. Resistance varies directly as the length of the conduit is increased, with a reciprocal change in the pressure drop across it. Considering the relatively long route through small arterial channels which blood must traverse to reach the heart through the pedicles of skin, muscle, jejunal, or stomach wall, it seems hard to imagine that the pressure would still be above that in the coronary arteries if the rate of flow were up to significant levels. The Vineberg procedure is in contrast with these other pedicles because it uses a relatively large vessel with high pressure which carries blood to a point very close to the coronary arteries.

In order to prove the outlined hypothesis experimentally it is necessary to have a near normal pressure in the arteries in the pedicle, and also to have an abnormally low pressure in the coronary arteries. This latter requirement has proved to be a very difficult problem for experimentalists. A major coronary artery, usually the anterior descending, has been ligated in the dog. Vineberg and associates[36] and others have reported better results when their pedicles were placed on dogs in which this was done. The objections to this method for producing a coronary hypotension are that there is likely to be a rather high operative mortality, and if the dog survives there is likely to be death of muscle and replacement by fibrous tissue so that there is little "run off" for arterial blood. The timing also is critical because intercoronaries from the dog's own heart assume significant proportions within 5 to 7 days, and probably restore the arterial pressure to near normal in the region distal to the ligation.

A somewhat better experimental preparation has been obtained with the ameroid.[11] This is a gradually expanding device which produced an occlusion of the coronary artery over a period of several weeks. A similar device used by the author consisted of a small expanding plastic bag inside a sleeve around the coronary artery. The difficulties encountered with this technique included a mysterious sudden death which occurred between the 4th and 6th days in about 30 per cent of the dogs which was perhaps a form of "mechanism" death. A similar phenomenon was described by Vineberg.[11] There was a great tendency for the circumflex to provide intercoronary collaterals after this type of occlusion of the anterior descending artery, although the right coronary rarely contributed any channels which were demonstrable by corrosion cast technique.

It was possible to place a second expanding bag on the circumflex artery 7 to 10 days after the first one was put on the anterior descending, but the high mortality and the critical timing necessary made the procedure rather unsatisfactory.

The present technique takes advantage of the principle of gradual occlusion of a major artery which is large in relation to the amount of blood that normally flows through it and, therefore, normally has a very small pressure drop from one end to the other. The distal pressure in such an artery shows very little or no change until the diameter of a short constriction is reduced to perhaps to 30 or 50 per cent of its original value, and then the distal pressure falls very rapidly with further small decreases in the diameter. The left main coronary artery has been used to surmount the problem of intercoronary collateral channels from the circumflex bringing in blood which can correct the hypotension when only the anterior descending is obstructed. The constriction is done by twisting a fine piece of copper wire around the left main coronary artery while distal pressure is continuously monitored by a needle in the circumflex. The wire is tightened until the diastolic pressure begins to fall, at which time there is seen a more rapid fall off in the pulse wave after the systolic peak is passed. Apparently, reaction to the copper wire decreases the diameter a little further as time progresses and thus slow, gradual occlusion through the critical phase is achieved. The dogs have consistently died with congestive failure several weeks to several months later, and the the technique appears most promising.

Assuming now that a pressure difference can be produced between the coronary artery and the arteries in the pedicle, the second requirement of the hypotheses must be met. There must be a vascular communication between them. Newly formed capillaries in granulation tissue between the pedicle and the heart are the only communications available. An important question, therefore, is whether these capillaries will satisfy the requirements of the hypothesis. There is some evidence that they can. Plastic surgeons can move a tubed pedicle graft up the body and nourish the graft through collateral vessels which cross what once was a suture line after the second end of the pedicle has been sectioned. Nevertheless, quantities of blood adequate to nourish skin may not help the myocardium and it is necessary to know the extent to which these vessels can be expected to develop under ideal conditions. As was recently reported at the Surgical Forum,[32] the thighs of dogs were divided except for the femoral arteries and veins, major nerves and femurs, and resuture was performed as in the original Halsted preparations. The femoral arteries were occluded at the same level 2 to 3 weeks later so that all of the arterial blood was forced through the original suture line.

There was no gangrene. Some of the dogs could walk on the involved leg after several days postoperatively. Post mortem arteriograms showed many arteries crossing the original site of division. The lumens were up to 0.3 mm. in diameter in dogs followed 2 or 3 weeks and were up to 0.7 mm. in those followed 9 weeks. Although a few channels of this size would not be of significant value, any of them probably would be.

Work done the same year (1955) demonstrated similar or perhaps larger collateral vessels between coronary arteries and the bronchial arteries of lungs with ligated pulmonary arteries.[21]

There are also some other basic points concerning pedicles which should be considered. To obtain maximal pressure gradient across the collateral channel, the pedicle must maintain a high pressure head while delivering large quantities of arterial blood to a point very near the coronary arteries. Our experiments support Vineberg's conclusion that collaterals from the mammary artery come only from pre-existing branches and cannot sprout directly through the arterial wall. Therefore it is wise to have as many branches as possible, and if the mammary artery can be transplanted close to the surface of the heart the short collateral channels will offer less resistance to the flow of blood. The surface seems preferable to a myocardial tunnel, because more coronary arteries are available there. A pedicle which would seem to embody these principles was made by dividing the mammary artery and vein about the level of the seventh intercostal space and elevating with them a strip of transversus thoracis muscle 1 cm. wide. Connective tissue between the vessels and muscles was left undisturbed and this tissue contained conduits for a small amount of arterial blood to flow from the artery to the vein. This flow of blood completely prevented thrombosis in the arteries and the tissue provided many small arterial channels to act as potential

sources for collaterals. The intercostal and other larger branches of the mammary artery were ligated with fine catgut, and the cautery was used for the smaller ones. The pedicle was wrapped around the left ventricle and sutured firmly to its surface. Preliminary observations are most promising and this type of pedicle has been demonstrated to be capable of forming many branches under favorable conditions.

Much more work must be done before the hypothesis presented in this paper can be applied to human beings. However, if the basic theory can be proved sound by animal experimentation, then logic would predict it would have a good chance of success on human patients. Studies have shown that many of the patients with symptomatic coronary arterial disease have partial or complete obstruction of one or more major or medium size coronary arteries. It is reasonable to assume that there is hypotension at the prearteriolar level in many arteries on the surface of the heart. A pedicle capable of delivering large quantities of arterial blood to a point very near the surface of the heart might well contribute significantly to the coronary arterial circulation beneath it if many moderate sized communications can be established between the two.

Collateral arteries have been repeatedly demonstrated between the two major coronary arteries in the human being when one is open and presumably has normal pressure in it and the other is obstructed and probably hypotensive. These intercoronary collateral channels would probably also form from the part of the arterial tree immediately under the pedicle to that in more distant regions of the heart. Adequate selection of patients will probably have to await satisfactory coronary arteriographic techniques.

The hypothesis presented in this paper would seem to be logical, and based on sound physiologic reasoning. Much more work is necessary to see whether it can be translated into actual benefit for the many patients suffering from this disease.

SUMMARY

Procedures for increasing the intercoronary collateral channels perhaps decrease the chances of sudden death from a subsequent occlusion of a coronary artery, but are not generally accepted by the medical profession as being of very much value. Often improvement in anginal pain occurs although perhaps temporarily. Approximately this same benefit has been reported after a ligation of the internal mammary artery and there is strong evidence that the latter does not increase the amount of blood available to the myocardium. Probably the relief of pain after both types of operative procedures is largely psychosomatic.

Pedicles designed to provide an extracardiac source of arterial blood, with the exception of the Vineberg operation, probably do not accomplish this purpose but may act as nonspecific irritation of the heart. The Vineberg pedicle probably does bring in more blood in some cases.

Review of the basic experiments on the physiology of collateral circulation formation reveals one common denominator which is present when collateral channels form and is absent when they do not. The basic conditions appear to be the existence of two pulsatile arterial beds with a difference in the pressures in them and a preexisting vascular channel between them. Experiments have shown that the latter need not be present since birth, and capillaries in newly formed granulation tissue across a suture line can develop into collateral channels of significant size.

A pedicle which can potentially deliver large quantities of arterial blood under high pressure with many suitable sites for the origin of collateral channels when sutured to the surface of the heart can be expected on theoretical grounds to form collateral channels to hypotensive coronary arteries, and there are preliminary observations suggesting that it will.

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THE MALIGNANT CARCINOID SYNDROME: MASSIVE LIVER RESECTION FOR SYMPTOMATIC RELIEF

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The malignant carcinoid syndrome has been the subject of a number of interesting papers appearing within the past few years in journals devoted chiefly to internal medicine, physiology, and biochemistry. Relatively few articles have appeared in the surgical literature concerning the newer knowledge of this unusual condition. Owing chiefly to the work of Thorson and associates[4] in Sweden and of Sjoerdsma and associates[2, 3] in this country, the medical profession is becoming much more aware of the bizarre and unusual symptom complex found in patients with a carcinoid tumor which has metastasized to the liver. The syndrome, in fact, appears to be a metabolic disorder of tryptophan metabolism. At the present time this symptom complex is not well understood. More attention has recently been given to this syndrome in the medical literature, which should lead to more correct diagnoses of the condition in the future.

This presentation emphasizes the clinical importance of the malignant carcinoid syndrome and presents what is believed to be the first demonstration of how a patient may be relieved of the severe and disabling vasomotor disturbances resulting from the presence of malignant carcinoid tissue in the liver. It will be pointed out that a massive removal of functioning metastatic carcinoid tissue from the liver can produce a marked decrease in the serotonin level. An abnormally high serotonin level resulting from functioning malignant carcinoid tissue growing in the liver can cause severe changes in the right side of the heart. Since this serotonin level can be reduced by massive liver resection, it is emphasized that surgical treatment in such cases may greatly prolong the patient's life by preventing or delaying the development of abnormal changes in the right heart.

CLINICAL FINDINGS

An individual suffering from this disease frequently is subject to recurrent attacks of diarrhea, associated with severe cramping abdominal pain. These symptoms are easily understood since such patients usually have the primary tumor or tumors located in the small intestine. Some of these patients also have evidence of bronchial constriction and symptoms which suggest the presence of asthma.

Perhaps the most bizarre and the most spectacular symptoms presented by patients suffering from the malignant carcinoid syndrome, are those symptoms which are associated with the very severe vasomotor reactions which these patients exhibit at various times. The patients are prone to have attacks of severe "hot flushes" which involve the face and neck and may involve the entire upper half of the body. During such a "hot flush", the patient frequently feels very weak and is also troubled by severe palpitation. These hot flushes may be associated with a fall in blood pressure and faintness, and in some instances, the attacks are so severe that they produce syncope. It is important to realize that in a number of individuals hot flushes and a fall of blood pressure to a shock level may be produced by palpation of the malignant carcinoid tumor in the abdomen. It is believed that these symptoms are produced by a sudden increase in the circulating serotonin which results from palpation of the malignant tumor.

Patients suffering from malignant carcinoid tend to develop pathologic changes in the right heart, which eventually may result in heart failure; the patient may actually die of heart failure before the malignant disease runs its course. Apparently the circulating hormone, serotonin (5-hydroxytryptamine), causes a thickening of the endocardium and subendothelial tissues of the right side of the heart. This eventually results in tricuspid and pulmonary valve insufficiency and stenosis. Autopsy studies have demonstrated the presence of fibrosis of the valves of the right heart in such cases. It is interesting that such changes in the heart apparently occur only in cases where the metastatic tumor is present in the liver or where the serotonin produced by the tumor can enter the general circulation without going

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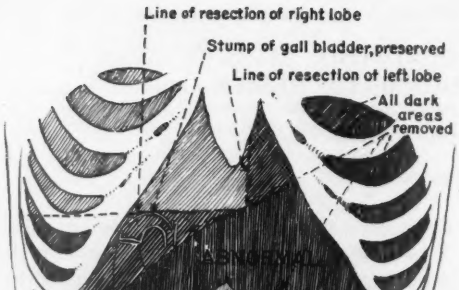
Line of resection of right lobe
Stump of gall bladder, preserved
Line of resection of left lobe
All dark areas removed
MESENTERIAL

FIG. 1. Drawing illustrates greatly enlarged liver and shows lines of resection used to remove 1182 gm. of liver tissue from the right and left lobes. Primary tumor in terminal ileum with regional lymph node involvement also indicated.

through a normal liver. Thus, it is generally held that the serotonin produced by a malignant carcinoid is usually "detoxified" in the liver. However, when the tumor itself is growing in the liver and serotonin enters the general circulation directly, as by way of the ovarian vein, then changes may be expected to occur in the right side of the heart. It is still not entirely clear just why the serotonin produces such changes only in the right side of the heart. There is some evidence also that the lung may tend to counteract the changes which may be produced by serotonin. However, this phase of the problem is still not clear.

LABORATORY DIAGNOSIS

It is important to realize that the clinician has a simple and easily run laboratory test which will demonstrate the presence of this type of malignant disease. Serotonin is a metabolite of the essential amino acid, tryptophan. In patients having the malignant carcinoid syndrome, serotonin is greatly increased in the circulating blood. Serotonin, or 5-hydroxytryptamine, is broken down by the body into 5-hydroxyindolacetic acid (5-HIAA) and it is this material which can be so easily demonstrated in the urine by a simple colorimetric qualitative test. The 24-hour qualitative measurement of the 5-HIAA in the urine may also be determined without great difficulty. Sjoerdsma,[2, 3] has made numerous determinations of the serotonin level in malignant carcinoid tumors removed at operation or at autopsy.

DISCUSSION

We have had occasion to see 3 patients who have had malignant carcinoid syndrome. In case 1 the patient, who was believed to be in the last stages of metastatic malignant disease of the liver, was found by his internist, Dr. Phil Orphet, and by the author to be suffering from the malignant carcinoid syndrome. It was our feeling that if the very distressing symptoms were being produced by malignant carcinoid tissue growing in the liver, more changes in the heart and eventual heart failure might result. The only chance of saving the patient's life seemed to lie in not only removing the primary tumor, but also in decreasing the amount of the circulating serotonin by the removal of a very large amount of the malignant tumor from the liver. We felt that even if it were not possible to completely remove the malignant carcinoid from the liver, that a subtotal removal of the malignant carcinoid might greatly decrease the amount of circulating serotonin in the blood. This might be considered somewhat analogous to the situation which confronts the surgeon when a patient's heart is being overworked as a result of hyperthyroidism. By removing a large amount of the thyroid gland, one can greatly decrease the amount of thyroid hormone which is circulating in the blood, causing the heart to be overworked. At the same time, in such cases, it is possible to leave the patient enough normal thyroid tissue to be compatible with a normal existence.

Case 1, we believe, is the first demonstration of how the symptomatology associated with this disease may be relieved by a massive resection of the liver. Cases 2 and 3 were patients in terminal stages of the disease and have been studied at autopsy.* Certain aspects of the problem and of the cases referred to are presented in more detail in other presentations.[1, 5]

* The autopsy in case 3 was performed by Dr. Too Kim.

CASE REPORTS

Case 1. M.B., a 41-year-old white man, entered the Baptist Hospital on July 15, 1956, because of severe diarrhea, weight loss, and symptoms of marked debility of 10 months' duration. The patient was experiencing from 6 to 10 stools each day. Previously he had been studied extensively at another medical center and his liver had been found to be markedly enlarged. The patient had been told that he probably had advanced malignant disease in the liver; laparotomy was not advised at that time. X-ray studies of the gastrointestinal tract were negative and had been negative on previous examinations. A number of liver function tests were performed and these appeared to be within normal limits. We performed an exploratory laparotomy through a short right subcostal incision. Both lobes of the liver contained metastatic tumor nodules varying from 1 to 6 cm. in diameter. A frozen section microscopic report was given as "undifferentiated carcinoma of the liver."

After leaving the hospital, the patient continued to have several watery stools each day and also began to be greatly troubled by severe flushing of the face, associated with weakness and palpitation. The patient's general condition, however, did not deteriorate as quickly as one would have expected with the findings shown at operation. Because of the bizarre flushing symptoms and the discrepancy between the patient's condition and the pathologic findings, Dr. Phil Orphet, the patient's internist, raised the question as to whether or not this patient might be suffering from the malignant carcinoid syndrome. Accordingly, determinations of 24-hour (5-HIAA) secretion were obtained. The findings, on 3 different days, revealed the presence of 553, 515 and 567 mg., respectively, of 5-hydroxyindolacetic acid (normal, 2 to 9 mg. in 24 hours). After reviewing the microscopic slides of the liver biopsy previously taken, the pathologist found them to be not diagnostic of the malignant carcinoid, but to be compatible with this diagnosis. It was our feeling that the patient had absolutely no chance of rehabilitation, without further surgery. We reasoned that it might be possible to relieve the patient of the severe "hot flushes" and to prevent or delay the development of heart failure by resecting a large amount of the malignant carcinoid tissue from the liver, thereby decreasing the level of circulating serotonin. It was, of course, also hoped that another search might reveal the primary tumor.

The patient was again hospitalized on February 14, 1957, and a second operation was carried out through a long modified bilateral subcostal incision. Small primary carcinoid tumors were found in the terminal ileum and a large mass of retroperitoneal lymph nodes was found in the mesentery which supplied this portion of the terminal ileum. The involved portion of the small intestine along with the metastatic lymph nodes in the mesentery were removed and the bowel continuity was re-established by end-to-end anastomosis. Following this, an extensive resection of the liver was carried out; almost the entire left lobe of the liver was excised. Bleeding was controlled by overlapping mattress sutures of 0 chromic catgut which were placed through the left lobe of the liver near its junction with the right lobe before the tissue was sectioned. Additional bleeding points were ligated individually. The gall bladder was then removed down to its ampulla and a catheter sutured into the ampulla and cystic duct. After this, a large amount of the right lobe of the liver was removed. The liver specimen weighed 1182 gm. Thus, an amount of liver which actually approximates the weight of a normal liver was removed. This procedure enabled us to decrease quantitatively the amount of malignant carcinoid tissue present in the patient's liver. We were fortunate in this case in being able to get accurate determinations of the serotonin level of the tissue removed.† The portion of terminal ileum removed, revealed the presence of six small carcinoid tumors. The pathologic report showed the tumors in the terminal ileum as well as the metastatic tumors in the liver to be carcinoid. During the first 2 postoperative days, the patient had several dramatic falls in blood pressure, to a shock level, which usually occurred when the patient was turned. We were never entirely sure whether these falls in blood pressure were related to absorption of abnormal amounts of serotonin or to an interference with the venous return, as a result of traction on the vena cava, during the immediate postoperative period. At the time of operation, in order to secure better access to the liver, it had been necessary to divide the supporting triangular ligaments of the liver. After the first few postoperative days, the patient began to make a remarkable recovery. It is interesting to note that the patient has apparently been entirely rehabilitated. He has almost entirely ceased having symptoms of flushing. He has gained 40 pounds and has been able to return to his work, managing a dairy. On numerous occasions, he has driven a

† These determinations, as well as the 24-hour urine determinations, were carried out at the National Institute of Health in the laboratory of Dr. Sjoerdema.

tractor and has been able to carry out other types of physical labor. The serotonin levels in the urine are still abnormally high. However, these levels are markedly reduced from those of the preoperative state.

Case 2. O.S., a 48-year-old colored man, was admitted to the hospital in August 1957. This case has been reported in detail elsewhere and only significant findings to emphasize the thesis of this presentation will be referred to here.[1] The patient clinically was shown to have the malignant carcinoid syndrome after a biopsy was performed to establish the type of tumor present in a metastatic nodule at the umbilicus. The patient also had a large mass in the right lower quadrant, an enlarged liver, symptoms of severe diarrhea and debility, and clinical changes in the right heart. Autopsy revealed changes of unusual interest in the right heart. The pathologist demonstrated the characteristic thickening and fibrosis in the endocardium and subendothelial tissues. There was definite thickening and shortening which involved the tendines and cusps of the tricuspid and the pulmonary valves. The patient had extensive metastatic carcinoid disease. The primary tumor, in this case, was located in the terminal ileum.

Case 3. E.G., a 54-year-old colored woman, was a patient in the City of Memphis Hospitals. Of special interest in this case, is the fact that she was shown to have the malignant carcinoid syndrome by a demonstration of 5-HIAA in the urine. At autopsy, the patient was found to have very extensive metastatic disease which involved the liver, diaphragm, gall bladder, common bile duct, pancreas, right adrenal gland, and the left kidney. No evidence of tumor was found in the gastrointestinal tract, although a very careful search was made of the entire intestinal tract. In this case, the primary carcinoid tumor was that which was found to have developed in the orifice of the right upper lobe bronchus. So far as we are aware, only four previous reports of cases of this type have appeared in the literature.

SUMMARY AND CONCLUSION

1. The malignant carcinoid syndrome is, in reality, a metabolic disorder of tryptophan metabolism.

2. Metastatic malignant carcinoid tissue in the liver produces abnormal amounts of circulating 5-hydroxytryptamine (serotonin) and this circulating hormone produces the severe "hot flushes" and other vasomotor phenonoma seen in these patients.

3. Patients with metastatic malignant carcinoid tissue in the liver are prone to develop symptoms of right heart failure as a result of subendothelial fibrosis and thickening which results from the abnormal serotonin level in the blood.

4. It is possible to decrease quantitatively the amount of circulating serotonin by a massive resection of the liver, thereby offering these patients a longer and more useful life than might otherwise be anticipated.

5. Cases are cited which demonstrate the other severe abnormalities, such as changes in the right heart, which may result from this syndrome when it is uncontrolled.

6. It is exceedingly important for surgeons, as well as internists, to become familiar with this metabolic disorder, in order that such conditions may be recognized and appropriate surgical treatment offered.

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THE RELATIONSHIP BETWEEN BREAST CANCER AND BENIGN BREAST DISEASE*

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The relationship between breast cancer and benign breast disease demands the keenest kind of critical appraisal. The strength of such a study rests upon the weakness of our current differential diagnosis and surgical treatment. Perhaps the significance of chronic cystic mastitis lies in the insignificance with which we so often regard it. I am sure that each of us can recall at least one patient in whom a perfectly benign breast lesion was successfully excised, only to be followed some years later by breast cancer well within the operative area. These striking examples of anatomical relationship seem to be a link that is "a little more than kin and little less than kind." However, one must not be beguiled into believing that a relationship exists merely because *post hoc, ergo propter hoc*—after this, therefore because of this. The pitfall of this kind of presumptive reasoning lies within the very shadow of truth.

The term benign breast disease enfolds in its indiscriminate embrace a galaxy of "synonyms" all of which are in common use and many of which describe variations of the same clinical condition. A strange, complex and hybrid glossary such as fibroadenosis, fibrocystic disease, blunt duct adenosis, chronic cystic mastitis, mastopathy, Reclus' disease, sclerosing adenosis, Bloodgood's blue-domed cysts, mazoplasia, Schimmelbusch's disease, mammary dysplasia and others are oft repeated in the literature, thus adding chronicity to confusion.

Although the name "chronic cystic mastitis" is considered objectionable by such distinguished pathologists as Foote and Stewart[3] because "it conveys no indication of the presence or absence of many characteristic histopathologic changes, moreover, it implies a common etiology for a variety of lesions most of which are anything but basically inflammatory processes," yet clinically the name is useful even if not pathologically precise or strictly descriptive. In the United States, at least, chronic cystic mastitis is understood by all, advocated by authority and recommended by custom. For the purpose of simplicity the term chronic cystic mastitis as used in this discussion will include fibroadenoma, cystic disease, adenosis, intraductal hyperplasia and papilloma as the predominant pathologic lesion.

Our own clinical investigation[10] of this problem constituted a long-term follow-up survey of all patients operated upon at the Johns Hopkins Hospital for chronic cystic mastitis between 1925 and 1941, inclusive. During this period there were 451 patients who underwent surgery and 385, or 85 per cent, were successfully followed over a 1- to 25-year period. The operation performed was predominantly local excision, however, some patients had a simple mastectomy and a few had a radical mastectomy. Over the course of years a total of 7 out of 385 patients, or 1.8 per cent, subsequently developed breast cancer after a follow-up period varying from 8 to 18 years. It is of some significance to note that 4 of these 7 patients developed cancer in the contralateral breast. When compared to the "normal" expected incidence of breast cancer in women of a similar age range and followed over a comparable period of time, this present group of chronic cystic mastitis patients appeared to develop breast cancer 2.6 to 3.6 times as frequently.

These results are in close accord with parallel studies of Warren[16] in Boston, Clagett and associates[1] at the Mayo Clinic, Haagensen and Stout[15] of the Presbyterian Hospital in New York and Kiaer[8] of Copenhagen. The breast cancer incidence for women with pre-existing benign breast disease was found to be 4.5 times as great as expected in Warren's series, 5 times as great in Clagett's series and 4 times as great in Haagensen and Stout's series. In Kiaer's excellent monograph on this subject, he followed 321 patients with histologically proven "fibroadenosis" for an average period of 17 years in one group and 11.7 years

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in another and found an actual incidence of breast cancer 4 to 5 times higher than was to be expected. The similarity of these clinical results reveals a striking and significant uniformity.

However, in the natural history of breast cancer the evidence of relationship to chronic cystic mastitis must be carefully explored in a broad clinical and experimental orbit before coming to a final countdown.

The pioneer experimental studies of Goormaghtigh and Amerlinck[7] revealed cystic changes in the mouse breast after prolonged estrogen stimulation. The classic work of Lacassagne[9] indicated that changes characteristic of chronic cystic mastitis were often a precursor to breast cancer which could be produced in mice in response to estrogens. Geshickter[6] noted that estrone administered to rats over a long period of time produced adenosis and cystic changes in the breast. In a group of carefully conducted experiments Pullinger[13] demonstrated that estrogen alone could produce duct-acinar distention without the ancillary action of progesterone or prolactin. Moore and associates[12] did serial breast biopsies in men treated with stilbestrol for cancer of the prostate and they all revealed changes characteristic of chronic cystic mastitis. Thus, I think it is safe to say that excessive estrogen stimulation plays an important role in the production of chronic cystic mastitis. Whether this relative hypterestrinism is truly a preponderance of estrogen or a deficiency in estrogen antagonists such as progesterone remains to be determined. Such careful investigators as Womack[17] and Copeland[2] favor the view that an anovulatory menstrual cycle leads to a deficiency of progesterone resulting in a prolonged and unopposed period of estrogen stimulation.

There is, of course, extensive experimental evidence in animals which indicates that the development of breast cancer also requires estrogen stimulation as one of its essential prerequisites. Similarly, there can be scarcely any doubt that estrogens are of equal importance in the development and progress of human breast cancer. Those of us who have had the opportunity of observing patients with advanced breast cancer recognize that a large number of these tumors are hormone stimulated. Palliative management of these patients is directed to altering the endocrine environment by means of castration, the sex steroids or endocrine ablation procedures.

Clinically, of course, there is much to suggest that chronic cystic mastitis is at least hormone responsive if not dependent as it is frequently found in the premenopausal period when the crescendo of normal endocrine activity is on the wane. It is most common in childless or unmarried women and is often related to menstrual irregularity, infertility and anovulatory menses, as well as to the endocrine imbalance associated with stress and emotional tension. Premenstrual mastodynia, engorgement, sensitivity and swelling are usually aggravated by estrogen administration and may be relieved by androgens or a progestogen. Following the menopause the severity of this symptom complex gradually subsides.

The histopathologic observations of Sommers[14] in a series of women with breast cancer are of special interest and indicate the presence of frequent abnormalities in the endocrine glands, particularly pituitary and ovarian hyperplasia. Sommers states that "so far as morphologic observations permit interpretation, about two-thirds of the 207 women with breast cancer gave evidence of a prolonged estrogen stimulation of the endometrium and breast."

No doubt the best proof of the causal relationship between chronic cystic mastitis and breast cancer would be the simple and direct histologic demonstration that the point of neoplastic departure begins in a nidus of benign breast disease. Foote and Stewart[3] confidently say "that we have seen cancer begin in duct papillomatosis, solitary and multiple, cyst, apocrine and epithelium and blunt duct adenosis." In a careful review of the literature one can find many proponents of the "evolutionary" theory who seem charmed by the mystical transformation of epithelial hyperplasia to neoplasia. Kiaer[8] found morphologic transitions to be particularly common in the more pronounced grades of "fibroadenosis." The transition passed gradually from duct adenosis to duct carcinoma which ultimately became invasive.

However, it must be remembered that the pathologic picture of chronic cystic mastitis is an exceptionally common condition even in "normal" women. In a special study of the breasts of 225 routine autopsy cases where there was no previous history of breast disease, Frantz and colleagues[5] found the frequency of breast abnormality to be high. The actual incidence of latent chronic cystic mastitis was observed to be

53 per cent. Kiaer found that 33 per cent of clinically "normal" breasts examined at autopsy showed latent changes which were histologically indistinguishable from manifest cases of chronic cystic mastitis. However, in patients with breast cancer these associated cystic changes were twice as common and showed a very marked and pronounced degree of epithelial proliferation.

In an interesting follow-up study performed perhaps by putting the cart before the horse, Foote and Stewart[3] reviewed the records of 1200 patients with operable breast cancer and found a previous history of operation for benign breast disease in 2.5 per cent. A control group of 1200 patients with cancer elsewhere in the body was reviewed and the incidence of benign breast disease was only 1.1 per cent or less than one-half as much. The histologic appearance of the chronic cystic mastitis was not correlated with the subsequent development of breast cancer.

However, it seems obvious that an accurate and precise differential diagnosis between benign epithelial hyperplasia and malignant epithelial neoplasia is urgently needed. Whereas it has been said by that distinguished French novelist Anatole France that "the future is a convenient place for dreams," a recent report by Louis[11] of the University of Melbourne, Australia, holds out hope that "what will be, is!" He studied breast tumors by a new staining technique and found a clear distinction could be made between normal and malignant cells using his globulin-fluorescein complex stain. Normal epithelial cells stained well (the fluorescence was demonstrated by ultraviolet light) but malignant cells did not stain at all. The author compared epithelial proliferation in several types of chronic cystic mastitis with breast cancer and found the method to be infallible in its accuracy. In 35 cases of breast cancer there was no evidence of fluorescent staining and in 36 cases of benign breast disease all epithelial elements stained well. If confirmed, this unique and significant observation would indicate that the biologic behavior of the benign epithelial cell of chronic cystic mastitis is qualitatively different in its chemical affinity from the malignant epithelial cell of carcinoma. The originality of this new development may be the forerunner of many important and exciting discoveries in the field of cancer research.

The natural history of breast cancer is extremely difficult to trace. However, the formidable task of recognizing the earliest stage in neoplasia may be greatly facilitated by fluorescent staining. Malignant change is probably a dynamic process as noted by Foulds[4] "advancing through stages that are qualitatively different." The decisive steps in this process are the result of progression, which can be best defined as an irreversible qualitative change in the character of the individual cell. Although chronic cystic mastitis may progress in many diverse ways to breast cancer, the steps in this sequence are neither automatic nor inevitable. The lesions along the varied path to malignancy are called "precancerous" or "potential precursors of cancer" but as Foulds observes they are not necessarily predestined to develop into cancer. Actually they are much more likely to persist as various types of chronic cystic mastitis or even regress altogether. However, the new property acquired by the cancer cell in its qualitative and irreversible transformation may now be visibly recognized for the first time by fluorescent staining. With this divining rod "the glories of the possible are ours" for the future.

In summary one may say that there does exist a basic relationship between breast cancer and benign breast disease. Certainly the experimental evidence indicates that an endocrine environment prevails which is conducive to the development of both chronic cystic mastitis and breast cancer. The histopathologic studies are strongly suggestive; and the follow-up clinical statistics are indeed most impressive. In the natural history of breast cancer, chronic cystic mastitis may be only one of several diverse directions in the development of malignancy. The steps of this sequence are discontinuous and are still largely dependent upon the defenses of each individual.

In conclusion the teachings of Sir Astley Cooper written 130 years ago are still appropriate as a source of inspiration for our present day practice:

> Though no specific remedy may yet have been discovered for the cure of some diseases, it is still a great advantage to be able to discriminate curable from incurable cases; the dangerous from the slight; those which require surgical operations from those which do not demand them; and such as admit of a trifling operation from those which call for one of extreme severity.

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STUDIES ON HEALING OF ANORECTAL WOUNDS*

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Although many more operations are performed on the anorectum than on the heart, in the average general hospital, many more articles appear dealing with cardiovascular than with anorectal surgery. This disproportion in the surgical literature mirrors the relative degrees of productive investigation and the relative rates of progress of these two surgical subspecialties.

Traditionally, mores and prudery have handicapped the study of lesions of the anorectum. Furthermore, because there does not seem to be any esthetic appeal, studies of the anorectal region do not readily attract investigators and, what is also important, funds for research. Because lesions of this region are quite common, often painful, and many times serious, they merit more investigation than is now presently being conducted.

Several years ago, a program to study postoperative anorectal wound healing was set up at the Medical College of South Carolina because the need for more research in proctology was realized. In this project, each case was documented by serial color photographs to provide objective evidence and to communicate information more accurately. This is an innovation in anorectal investigations. These color photographs possess inestimable value and provide the data for this clinical report.

Such well known and generally accepted factors affecting wound healing, *i.e.*, nutritional status, vitamin intake, protein requirement, blood supply, fluid and electrolyte balance, will not be discussed in this paper. There are, however, special features that characterize the healing and, also, hinder the study of anorectal wounds, namely: inaccessibility, lack of immobilization, and contamination. At the passageway of countless microorganisms, contamination is a factor in wound healing. Fortunately, contamination does not always result in gross signs of infection. Moreover, the range of influence of this contamination is not fully known.

In an attempt to reduce further the effect of bacterial contamination of surgical anorectal wounds, orally administered erythromycin and tetracycline and locally applied nitrofurazone were used in this study program.†

The clinical material was classified in groups in chance manner, *i.e.*, there was no arbitrary way of classifying a case that would "weight" the results. One group of 17 patients received erythromycin, a second group of 14 received tetracycline, and a third group of 15 received no antibiotic and served as a control.

Performed by the same operator, the operations included hemorrhoidectomy, fissurectomy, and fistulectomy, either singly or combined. The hemorrhoidectomy was a modified ligature excision open type. The fissurectomy was a modification of the type described by Gabriel.[2]

The oral dose schedule used for erythromycin, was 400 mg. q.i.d.; for tetracycline, 250 mg. q.i.d. In all cases the therapy was started within 4 hours after operation. To be certain that the patient received the prescribed medication on schedule, the drug was given postoperatively throughout the entire hospital stay which ranged from 3 to 7 days; the average being 4.5 days. Each wound was photographed in color before and immediately after the operation, and at weekly intervals thereafter until healed.

To analyze the results, case records and color slides were carefully reviewed. Repeated viewing of the color slides permitted close examination of all phases of wound healing. Careful study and comparison of the cases in the three groups showed no significant variations. When compared at the same postoperative intervals, no discernible difference in wound appearances of the three groups could be found. Furthermore, the anti-

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* The erythromycin used in this study was Erythrocin, supplied by Abbott Laboratories, and Ilotycin, supplied by Eli Lilly and Company. The tetracycline used was Achromycin, supplied by Lederle Laboratories Division, American Cyanamid Company, and Tetracyn, supplied by Chas. Pfizer and Company. The nitrofurazone used was Furacin soluble dressing supplied by Eaton Laboratories.

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biotics did not decrease the need for analgesic medication.

Since antibiotics, orally administered, did not significantly promote wound healing of the anorectum, a topical antimicrobial agent, nitrofurazone, in a water soluble ointment, was studied on a similar basis on hemorrhoidectomy and fissurectomy wounds. Nitrofurazone, highly effective against the common bacterial flora of wounds, has lately been gaining increased recognition in wound therapy. Many clinical studies attesting to its effectiveness in various types of superficial lesions, have been published.[1, 3-5]

Nitrofurazone, impregnated in a nonadhering rayon fabric gauze, was applied to the wound immediately after operation and during the 4- to 5-day postoperative hospital stay. Following discharge, the patient applied the nitrofurazone dressing daily for 21 days or until the wound was healed.

A control group of 40 patients was compared with 237 patients treated with nitrofurazone. Although the numbers of each group may seem out of balance, a careful comparison of the charts and color photographs revealed some definite differences in a significant proportion of cases. Generally, nitrofurazone treated wounds showed a cleaner granulating surface and less serous exudate. The wounds of the control group had paler granulating surfaces and more seropurulent exudate. The wounds treated with nitrofurazone seemed to heal more rapidly. Because there are inevitable differences in any two surgical anorectal wounds, even when the same operator and same technique are involved, it is difficult to make a more positive statement on this aspect.

Of the 237 patients on whom nitrofurazone was applied, there were only 3 cutaneous sensitivity reactions and these promptly subsided when the ointment was discontinued. These skin reactions, maculopapular lesions with pruritus, occurred when the drug was used for relatively long periods of time. One was a patient with an anal fissure and a nonspecific perianal ulcer with a relatively longer healing period; therefore, consequently prolonged treatment (58 days). In another patient, involving hemorrhoidectomy and fissurectomy, nitrofurazone was applied for 54 days, with development of a similar pruritic maculopapular skin lesion, which subsided on stopping the drug. The third, a patient with a fissurectomy, developed a similar pattern after 25 days. In the last 162 patients, in the series of 237, when nitrofurazone was discontinued by the 21st day, or sooner if the wound had healed, there were no such reactions to the drug.

That reduction of inflammation would decrease postoperative pain was the factor which initiated and motivated this study of anorectal wound healing. Wounds treated with nitrofurazone do look better and seem to heal better. However, there are other factors which reduce postoperative pain.

Before operation, briefing the patient and presenting a realistic appraisal is an important factor in preserving emotional stability. Retaining the patient's confidence is much easier than regaining it. An apprehensive patient tends to have a lower threshold for pain. Informing the patient of the various anticipated preoperative and postoperative events tends to prevent unnecessary anxiety and to remove much of the mystery of an anatomical area the patient cannot visualize.

Good anesthesia allowing full exposure is a keystone of good operative technique. My preference is low spinal saddle-block with tetracaine-dextrose. With modern retractors, the anorectum can be fully visualized and properly treated. Placing sutures in the rectal mucosa, which has an autonomic nerve supply rather than in the anal epithelium with its somatic nerves, is still another means of reducing postoperative pain. Nonadhering gauze provides another means of minimizing discomfort. Even before the anesthetic begins to wear off, administration of a narcotic tends to delay the development of pain.

None of the above mentioned aids alone significantly minimizes pain. However, in concert, all of the above measures work together to effect analgesia. To use an analogy, just as a top flight football team earns its reputation by displaying excellence in the fundamentals of tackling, passing, running and blocking, even so a satisfactory anorectal operation is the result of attention to all these fundamentals of good surgical technique and care.

SUMMARY

Some results of clinical studies of anorectal wound healing have been reported. Neither erythromycin, 400 mg. q.i.d., nor tetracycline, 250 mg. q.i.d., administered orally for 3 to 7 days significantly promoted wound healing. However, nitrofurazone topically applied daily had a demonstra-

ble beneficial influence on healing, *i.e.*, cleaner granulating surface and less exudate. The reduction of pain following anorectal surgery is not the result of any one factor. Pain is minimized by the intelligent application of the many basic principles of surgical technique and care.

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SOME PROBLEMS IN OPEN HEART SURGERY*

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The introduction of extracorporeal circulation has created extraordinary conditions never before experienced. After a decade of clinical and experimental research, many problems are still controversial. In our early medical education we learned to understand the complicated signal system of the human body. We learned to evaluate the complex biochemical changes in the blood. We knew when the pulse was normal or abnormal, what the desirable body temperature and blood pressure were, and what it meant if the patient was pale or cyanotic. We could recognize whether the patient was well or his life was in danger.

The situation is entirely different when the patient is on cardiopulmonary bypass. We then deal with an individual who does not breathe, has no heartbeat, and whose temperature may be abnormally low. We actually do not know whether he is alive or dead, nor whether we are going to restart the heart of a living person or resuscitate a corpse. The burning problem in open heart surgery is not to invent a new machine but to discover the "normal" of the abnormal and to establish new biologic standards in this extraordinary condition. Now, we are only able to guess the tolerable; we are far from knowing what the ideal is.

Trying to determine which is the best oxygenator is very difficult, if not impossible. The wide variation in operative indication and technique makes the clinical evaluation very complicated. It is common for the surgeon, with his very early cases, to blame the heart-lung machine for his poor results. Then he switches from one oxygenator to another, and finally his operative technique and clinical judgment improve. Thereafter he is happy with the particular type of oxygenator on hand.

The failures of any new team are usually the consequences of the following mistakes.

1. In the beginning it is due to the incompetence and/or improper monitoring of the heart-lung machine.

2. Later, the majority of deaths are caused by mistakes in surgical technique.

3. Finally, the failure of the operation is due to mistakes in operative indications.

There are about 24 different pump oxygenators in use which can be catalogued into three large groups: (1) the screen and film oxygenators (includes the rotating disc) in which oxygen is exposed to a thin, large surface area of blood. (2) the "bubblers," in which oxygen is bubbled into the blood; and (3) the membrane oxygenator, in which blood and oxygen are separated by a semipermeable membrane across which oxygen passes.

Despite the important role bubble oxygenators played in the development of open heart surgery,[13] they are becoming outmoded. The antifoam agents, the increased hazard of gas embolism, and the fact that the system is wide open are disadvantages which make them less popular.

Theoretically, the membrane oxygenator[3, 14, 15] should be the most physiologic, and less traumatic, and we are convinced that within a few years this principle in cardiopulmonary bypass will be the most generally accepted. However, at the present time the difficulties in handling it, the large size, and the disproportionally low oxygenation are disadvantages which seriously impede the wide acceptance of this ingenious machine.

It is our opinion that as the bubbler was the oxygenator of the past, the filmer is the oxygenator of the present,[12] and the membrane will be the oxygenator of the future. The filmers are relatively small, efficient, easy to handle and to sterilize. The rotating disc oxygenator† at the

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† Manufactured by PEMCO, Inc., Cleveland, Ohio.

present time used in our institute,[16] is a variety of this group. This machine was originally developed by Björk[1] in Sweden, but popularized in this country by Cross and associates.[5] A film of blood is picked up by a series of rotating discs and is passed through an atmosphere of oxygen. We have found this instrument to be highly efficient and relatively atraumatic. During the last year we performed our open heart operations with this type of filmer, exclusively.

MONITORING OF HEART-LUNG MACHINE

There is considerable confusion regarding monitoring the pump in extracorporeal circulation. Different groups observe, record and use as a guide, various physiologic events.[2, 11, 15, 16, 17] In some operating rooms the electroencephalogram is used; in others, the pH determination dominates, whereas another group would refuse to perform open heart surgery without receiving continuous information about the oxygen and carbon dioxide tension. Actually, however, there is no controversy, since we are all seeking information concerning the effectiveness of the perfusion and the condition of the patient. These changes are corelated closely. Each is using the language that he understands best; or rather, using the gadgets and methods he is most familiar with to obtain the necessary information.

In monitoring the machine and regulating the blood volume, our group is quite satisfied with continuous observation of the electrocardiogram, arterial and central venous pressure, and the blood flow.

FIG. 1. Artificial heart-lung Machine used in our open heart operations

The purpose of the artificial heart-lung machine is to replace these two organs temporarily, and it must do this completely.[4, 8] We use the calculated normal resting cardiac output of the patient for blood flow through the machine. In children and young adults we are able to do this without difficulty. The rotating disc oxygenator provides 95 per cent oxygenation, up to 3000 cc. per minute blood flow, and the hemolysis remains less than 1 per cent after 30 minutes of perfusion. We see no reason to use the low flow principle with or without hypothermia.

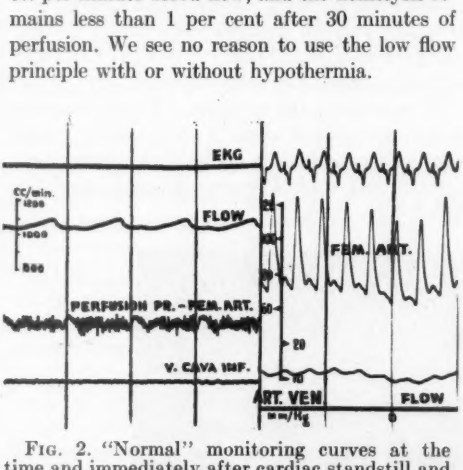

FIG. 2. "Normal" monitoring curves at the time and immediately after cardiac standstill and cardiopulmonary bypass.

Artificial cooling of the body makes the tissues tolerable for a short term anoxia. In extracorporeal circulation, when the patient is anoxic, hypothermia is not needed but sufficient oxygenation of the blood is. If he is not anoxic, the simultaneous use of hypothermia and the heart-lung machine is similar to the man who wears suspenders and a belt but who may still lose his trousers!

The most important data regarding the performance of a successful cardiopulmonary bypass is the blood flow itself. Two methods of estimating blood flow have been employed; one is the use of a venous reservoir as a flowmeter, and the other is calibration of the pumps and calculating the flow from the revolutions per minute quotient. These methods are inaccurate and may have serious disadvantages. They indicate normal or even increased flow when the blood passing through the system is seriously impeded.

Recently, several attempts have been made to design a reliable flowmeter, but none of these complicated and expensive instruments have become popular. During the past 3 years we have experimented with different types of flowmeters. The instrument which most closely approximates the ideal criteria is the orifice plate flowmeter.

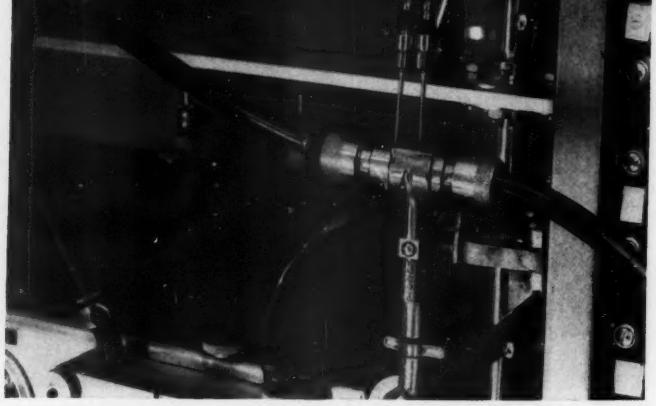

FIG. 3. The orifice plate flowmeter

This instrument, developed in our laboratory,[18] uses the pressure differential caused by a mild constriction of the fluid conduit to infer the rate of flow. The primary element is the orifice plate itself, and the secondary element is a device for measuring and recording pressure difference. In this way the pressure difference, measured and calculated, can be directly expressed as flow, in cubic centimeters per minute. This simple device is used routinely in our open heart operations. It is made of silicone coated stainless steel and weighs less than 200 gm. It is our belief that its introduction has increased significantly the safety of open heart operations.

OVERDISTENTION OF HEART

Recently, special attention has been given to the syndrome called "overdistention of the left ventricle."[7] This syndrome manifests itself as acute heart insufficiency immediately following cardiopulmonary bypass. The failure of the heart is the consequence of a serious and sometimes irreversible damage of the heart muscle caused by excessive stretching of myocardial fibers. It is our experience that the right ventricle, which is already under strain in most of the cases before surgery, is no less sensitive to overfilling than the left; therefore, we prefer calling the syndrome "overdistention of the heart."

This syndrome can be differentiated into three forms: (1) hypervolemic, (2) atonic, and (3) obstructive.

Hypervolemic overdistention. This form of the syndrome is due to an abnormal increase of circulating blood volume. The mechanism is similar to the well known picture of the "overtransfused heart."[6, 9, 10] It is often accompanied by changes in other vital organs, such as cerebral edema and pulmonary congestion. Small subjects with elevated pulmonary vascular resistance are especially sensitive to such an overload.

Hypervolemic overdistention is commonly caused by the following technical errors: (1) incorrect calculation of blood flow during cardiopulmonary bypass; (2) in-coordination of the arterial and venous pumps; (3) undersized venous outflow cannulas; (4) inadequate venous suction or incorrectly positioned gravity reservoirs; (5) overestimation and overcorrection of blood loss; and (6) uncontrolled, multiple venous infusions.

Giving special attention to the above factors is the easiest way to avoid hypervolemia. The most sensitive indicator of hypervolemia is the elevation of the central venous pressure. This rise may be caused by other factors, but it always indicates a discrepancy between the blood volume and the pumping action of the heart. Following cardiopulmonary bypass, if the systemic arterial pressure is normal or even elevated, a rise in the venous pressure practically always means abnormal increase in the circulating blood volume, which requires immediate drainage of blood.

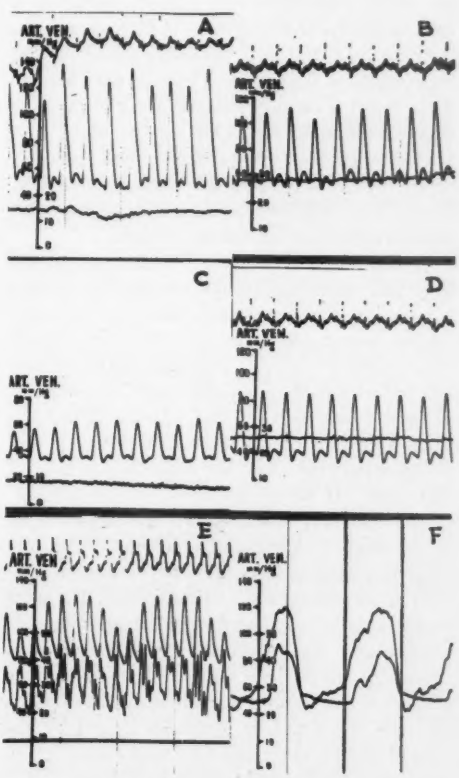

FIG. 4. Arterial and venous pressure tracings taken at the femoral artery and inferior vena cava immediately following cardiopulmonary bypass. *A*, optimal conditions, normal arterial and venous pressure, complete balance in the circulating blood volume. *B*, normal arterial and elevated central venous pressure indicating hypervolemia. *C*, severe hypovolemia. Low arterial and venous pressures. *D*, low arterial and elevated central venous pressure, suggesting acute heart failure with/or hypervolemia. *E*, moderately diminished arterial pulse pressure, high central venous pressure with great systolic-diastolic difference. Severe tricuspid insufficiency. *F*, severe bradycardia, abnormally high venous pulse pressure. Heart block, right ventricular failure with terminal tricuspid (functional) insufficiency.

If the systemic arterial pressure is below normal, elevation in the venous pressure may mean hypervolemia, right ventricular failure, or both. In the immediate postoperative period a careful check of the changes in body weight may give valuable information in the differentiation.

Atonic overdistention. If the extracorporeal circulation is discontinued before restoration of an effective heartbeat, atonic overdistention may be the result. Sometimes it is caused merely by a time element; not enough time is allowed between the removal of the aortic occlusion clamp and the interruption of the bypass. The same may happen if the heart is already beating, but the pump is stopped too suddenly. This can be easily prevented by gradually releasing the caval veins and proportionally decreasing the extracorporeal flow. In this way, sufficient time is given for the heart to reaccommodate its normal output.

In the absence of serious errors in surgical technique, prolonged cardiac standstill or ineffective contractions are consequences of severe myocardial anoxia due to air embolism or low perfusion pressure. Beck's principle that "nobody can restart a flabby, cyanotic heart" is valid also in open heart surgery. Prolongation of the bypass, elevation of the perfusion pressure, and patience may overcome the difficulties in most of the cases. If these measures are insufficient, gentle massage, electroshock, and injection of small doses of Adrenalin or calcium into the arterial perfusion line may be of considerable help in the restoration of the heartbeat. The same tactics have to be followed in prolonged ineffective contractions due to special sensitivity or overdosage of cardioplegic drugs. In some patients the heart just cannot accommodate the sudden changes in circulatory dynamics caused by the correction of the anomaly. In such cases, the reopening of the defect has to be considered.

Obstructive form of overdistention. The dangers of this complication have been recognized and widely discussed. Effler and associates[7] have described this syndrome and have outlined the management of this particular form localized to the left ventricle and pulmonary system. Even in complete bypass and cardiac standstill there is always some filling of the left heart from the pulmonary veins. This flow is especially high if the bronchial collaterals are rich, as in Tetralogy of Fallot.[16] Because of the dynamic or mechanical obstruction of the left ventricular outflow,

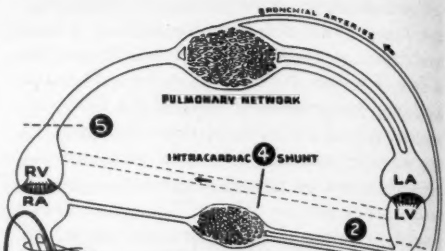

FIG. 5. Schema illustrating the possibility of the development of "overdistention" of the heart and the natural channels of decompression. The numbers mark the common places of artificial occlusion at the time of open heart surgery: *1*, constriction of the caval veins; *2*, "functional" occlusion of the aortic orifice by the perfusion pressure; *3*, cross-clamping of the ascending aorta; *4*, closure of a septal defect; *5*, cross-clamping of the pulmonary artery.

the danger of overdistention persists during the entire time of cardiopulmonary bypass.

In such abnormal conditions the atrioventricular valve never closes completely, and the ventricular overfilling always extends to the adjacent atrium. Knowing this, it is apparent that the easiest way to prevent left ventricular overfilling is to drain it through a catheter inserted into the left atrium. This is especially advisable in cyanotic heart disease where the bronchial collateral flow is sometimes enormous. However, the left atrial drainage is not imperative in most cases because there are channels through which the ventricles can be decompressed.

As long as the heart beats forcefully and the aorta is not clamped, there is no danger of overdistention even after the start of the cardiopulmonary bypass. It is advisable to start the perfusion 2 minutes before the induction of cardiac arrest. Thereby, the pulmonary vascular bed can be emptied and a considerable amount of blood saved. It is mandatory to open the heart immediately after the cessation of the heartbeat; otherwise, irreversible damage of both ventricular myocardiums may result.

While the cardiotomy wound is open, the dan-

ger of obstructive overdistention is small. The right heart is decompressed directly and the left heart, through the defect. Even after the closure of the septal defect, the left heart is still drained through the pulmonary vascular bed and pulmonary orifice. There are no valves between the left heart and pulmonary vessels; therefore, adequate drainage of the left heart could be expected at any point in the pulmonary system. The supporting evidence of this is that there is always oozing of red blood from the pulmonary orifice. The amount of drainage is proportional with the perfusion pressure and it is especially high in cases of well developed bronchial collaterals. It is mandatory never to cross-clamp the pulmonary artery together with the aorta. Other "safety valves" of less importance are the pulmonary-azygos venous communications and the coronary system.

The easiest way to prevent overdistention of the heart *after* the cardiotomy wound has been closed is to release the constriction of one of the caval veins. In this way the catheter drains not only the systemic veins, but also the heart. If the heart beats satisfactorily, the bypass can be gradually discontinued and the catheters removed, although it is a good precautionary measure to leave the arterial and one of the venous catheters in place temporarily so the bypass can be restarted or blood infused or drained if necessary.

OVEROXYGENATION

Overoxygenation is now getting a lot of consideration.[2, 7, 11] The undesirable effects of high oxygen tension were well known long before the era of open heart surgery. True enough, the usage of artificial oxygenators potentially increased this danger; however, it is our feeling that it has been somewhat overemphasized. The "overoxygenation of the blood," correctly expressed as "overoxygenation of the plasma," may lead to biologic disturbances in different ways, for instance that high plasma tension eliminates one of the biochemical impulses to breathe. This is of special importance in patients who are accustomed to chronic hypoxia because they become apneic, and the further accumulation of carbon dioxide in the blood leads to serious clinical symptoms. However, in the individual who is artificially ventilated, or is on cardiopulmonary bypass, this "high oxygen-high carbon dioxide" syndrome could not have any significance, since there is no need for spontaneous breathing.

Serious disfunction may result if the pressure of the oxygen gas in the oxygenator is considerably above atmospheric pressure, or if the patient's temperature differs significantly from that of the blood in the oxygenator. In either instance, the physically absorbed oxygen may be liberated from the oversaturated plasma, and multiple gas embolization of the vital organs may result.

Another danger of oversaturation of the plasma is that tissue cells may actually live on oxygen absorbed by the plasma and not depend on the biochemically bound oxygen of the hemoglobin. Under such conditions, the oxyhemoglobin content of the arterial and venous blood is equally high. This condition, namely absence of the reduced hemoglobin in the venous blood, interferes with the tissues-to-blood carbon dioxide exchange and with the formation of carbohemoglobin compounds. The result is carbon dioxide retention in the tissues and consequent damage of the enzymatic systems.

Effler and associates[7] called attention to the danger of using a large capacity oxygenator for the perfusion of small subjects. Such an oxygenator may "wash out" all the carbon dioxide from the blood. However, this is not really "oxygen poisoning"; the patient may suffer from severe alkalosis with all of its undesirable consequences. This could be easily prevented by using a 97.5 per cent oxygen-2.5 per cent carbon dioxide mixture, instead of pure oxygen, in the oxygenator.

We would like to emphasize that all these forms of "overoxygenation" are not common complications of open heart surgery, but inevitable consequences of faulty perfusion techniques or basically defective oxygenators. The solution of the problem is not a complicated laboratory technique to detect overoxygenation but to prevent it, which is very easily done by avoiding oxygen pressure above that of atmospheric pressure and by preventing discrepancies in the patient's temperature to that of the oxygenated blood.

DISCUSSION

Some of the problems peculiar to open heart surgery, to which special emphasis has been given in literature recently, have been discussed briefly. Many problems related to open heart surgery have already been solved but others, yet to be

recognized, will be our problems of tomorrow. It was 2 to 3 years ago when we worried about inadequate oxygenation, low flows and cooling of the patient; now, it is overoxygenation, overdistention and high temperatures. True enough, the experiences on which we have based this study are relatively limited. We think the best way to prevent and manage complications in open heart surgery is similar to that in any other field of surgery: (1) not to complicate but to simplify the procedure; (2) to maintain as closely as possible normal physiologic conditions; and (3) make use of the natural compensatory mechanisms of the human body since they are more efficient than the most sensitive man-made machine.

SUMMARY

The authors discuss some of the actual problems peculiar to extracorporeal circulation.

1. Experimenting with different types of artificial lungs, they found the rotating disc oxygenator simple, highly efficient, and relatively atraumatic.

2. In monitoring the heart-lung machine, continuous observation of electrocardiogram, flow and arterial and venous pressures is sufficient and advisable.

3. The purpose of pump oxygenators is complete temporary replacement of the heart and lungs; therefore, normal flow rates are preferable.

4. A new type of registering flowmeter is described.

5. The problems of preventing overdistention of the heart and "oxygen poisoning" are discussed in detail. Three forms of overdistention are differentiated: hypervolemic, atonic, and obstructive.

Acknowledgments. The authors are greatly indebted to the following anesthetists: Dr. J. C. Montgomery, Dr. Wm. B. Timmerman, Dr. Wm. Hamer, and Dr. Charles Chapman; also, to Mrs. Myra Stam and Mr. Emanuel Bagby, for their valuable technical assistance.

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SOME COMPLICATIONS OF SUBTOTAL GASTRECTOMY

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Gastrectomy, as in the case of a great many other operations of greater than average magnitude, was at one time performed fairly uncommonly in a comparatively limited number of hospitals by a relatively restricted group of surgeons. As a result of many evolutionary changes in treatment, hospitals and surgeons, gastrectomy is now a very common operation, frequently performed in the small community hospital and often performed by surgeons of necessarily limited experience. These considerations make it seem worthwhile to call attention to the fact that gastrectomy is still an operation of greater than average magnitude, one which for best results requires considerable technical skill and experience and one which may be attended by various complications, some serious, some less so. The complications incident to gastrectomy, whether performed for benign or malignant disease, may occur at the time of operation, during the immediate postoperative convalescence, or even long afterward.

At the time of operation, danger may lurk in anesthesia, contamination, hemorrhage and shock, damage to adjacent structures, disturbance of blood supply, poorly executed mechanical dispositions, and in improperly conceived physiologic arrangements. Complications during the immediate postoperative convalescence may include such remote things as a cerebral vascular accident, coronary artery occlusion, pneumonia, or such proximate dangers as peritonitis, leakage from the duodenal stump or the anastomosis, subphrenic abscess, internal hernia, intestinal obstruction, malfunction of the anastomosis, and hemorrhage. Complications occurring beyond the time of immediate postoperative convalescence include such things as the so-called dumping syndrome, a malfunctioning anastomosis, internal hernia, intestinal obstruction, stomal ulceration and other more remote possibilities.

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It is evident that in the above patently incomplete listing of the complications of gastrectomy some might be classified as impossible to prevent or even to anticipate. It is equally evident that some may be anticipated and either prevented or handled in such a way that mortality and morbidity may be minimized. It is to certain of this latter group of complications that this discussion will be addressed.

PREVENTION OF COMPLICATIONS

Avoidance, where possible, of gastrectomy performed as an emergency procedure in cases of hemorrhage and perforation and even obstruction will, in the essayist's belief, minimize both mortality and morbidity. Although various authors[3] have reported notable successes with gastrectomy as an immediate treatment of perforation and although hemorrhage will sometimes be fatal if not treated by gastrectomy as a surgical emergency, surely, in the long run, procedures of less magnitude than gastrectomy must be safer.[2] Recently, Elliott and associates[1] reported 16 per cent mortality in emergency operations for upper gastrointestinal tract hemorrhage as against 3 per cent mortality in elective and interval operations for hemorrhage.

The anesthesia employed and the duration of the operation are factors ancillary to the operation itself that still may be of great importance. Developments in anesthesiology have led, today, to depths of anesthesia bordering on the cadaveric. Agents to paralyze muscle, substitution of mechanical gas exchange for physiologic respiration, and other related factors have led surgeons trained in recent years to practically ignore operating time, often to the detriment of the patient. Doubling or trebling the duration of surgical trauma, the amounts of anesthetic agents, the requirements for fluids and electrolytes, the time of wound exposure to contamination and many other things, all functions of time, must surely enhance the possibilities of complications.

Concerning the operation itself, there are physiologic and mechanical problems that must be solved to prevent both immediate and remote

complications. Gastrectomies performed for malignant disease present some special problems, chiefly those related to the extent of the resection, as for instance, in total gastrectomy and resection of adjacent structures or organs. These will not be discussed as such. Exclusive of such special problems the surgeon must decide how much stomach to remove, whether to restore continuity by anastomosis of the gastric remnant with the duodenum or the jejunum, whether gastrojejunostomy should be antecolic or retrocolic, how large the stoma should be, whether the vagus nerves should be divided, and many lesser things too numerous to mention.

There are probably few if any surgeons who would disagree with the belief that the most radical subtotal gastrectomy reasonably possible is best for malignant disease. For benign disease, however, surgeons differ as to the best procedure. I believe that partial or subtotal gastrectomy, with or without vagotomy, and with restoration of continuity by a retrocolic short-loop gastrojejunostomy is best for most benign disease. Formerly we removed two-thirds to three-fourths of the stomach, but in recent years approximately one-half of the stomach. Bilateral vagal neurectomy as an associated procedure has been employed. Almost without exception the retrocolic anastomosis has been used. The lesser curvature part of the gastric stump is closed by suture, leaving the greater curvature part, 4 to 5 cm. in length, for the anastomosis, which is made with two rows of continuous atraumatic chromic catgut sutures. The afferent loop is from 5 to 10 cm. in length and enters the greater curvature side of the stoma. Subarachnoid block anesthesia has been used almost exclusively and the average operating time has been about 1½ hours.

No complete tabulation of complications attending personal gastrectomies has been made but over-all results have been satisfactory. In a period of 20 years, 1937 to 1956 inclusive, on my private service I have personally performed a total of 361 partial or subtotal gastrectomies; 312 for benign ulcerative disease; 49 for malignant disease. There were 8 postoperative deaths, giving an over-all mortality rate of 2.2 per cent.

Of the various complications which can occur, as partially listed near the beginning of this discussion, three have been chosen for special attention, namely: leakage from the duodenal stump associated with gastrojejunostomy, internal hernia beneath the afferent loop of a gastrojejunal anastomosis, and that peculiar disturbance of altered emptying of the stomach commonly called the dumping syndrome.

DUODENAL STUMP LEAKAGE

Leakage from the duodenal stump is a distressing complication which usually occurs within a few days of operation. The onset may be rapid but is usually not sudden. The patient becomes intensely and seriously ill. Pain, nausea and vomiting are early symptoms. Fever, tenderness, spasm and general deterioration are early signs. Laboratory and x-ray studies offer little that is positive but may help rule out other things. The normally convalescent gastrectomy patient whose picture changes as above must be suspected of a leaking duodenal stump though, of course, any other suture line leakage might present a similar clinical picture.

Once the diagnosis is made or even strongly suspected a local exploration should be made promptly. Otherwise generalized peritonitis may occur or localized abscess formation may develop in the subphrenic or subhepatic regions. As a matter of fact, these may develop anyhow but prompt drainage of leaking gastrointestinal, biliary and pancreatic secretions will minimize their occurrence or severity.

In dealing with the leaking stump, suture is not feasible because the tissues are so friable. Stump leakage occurred in the first place probably because the initial closure of the stump was difficult and inadequate and, therefore, a secondary closure would be infinitely more difficult and unsatisfactory. Rather than attempt closure that will be inadequate or in the attempt fail and produce a duodenal fistula larger than before, one may make use of a special drainage procedure (fig. 1). If properly accomplished and well managed it will keep the wound healthy and so eventually promote spontaneous closure of the fistula. This is sump drainage; a drain within a drain, the constant sucking of fluid drainage from a sump well in which it collects and from which it is removed as fast as it accumulates, thereby keeping the area constantly dry or nearly so. Soggy dressings with consequent wound digestion are avoided.

The large amounts of fluid and electrolytes aspirated are collected and measured and together with appropriate tests of the patient's

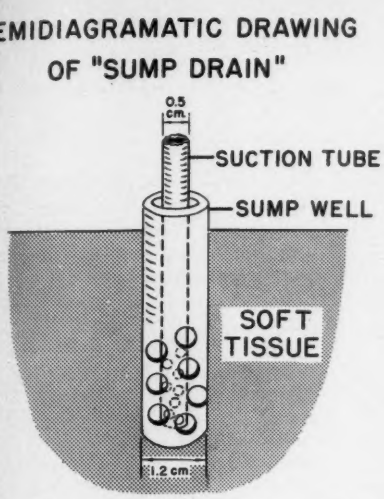

FIG. 1. Diagram; principle of the sump drain

blood, make it possible to maintain him in normal fluid and electrolyte balance. Blood transfusions and antibiotics may be helpful. Sometimes food by mouth may be tolerated reasonably well. Tube feeding, the end of the tube well down in the efferent loop of the anastomosis, may be helpful. If the duration of the fistula should be short, nutrition may not be a serious problem; otherwise it may be a very serious one.

Obstruction of the afferent gastrojejunostomy loop may have been a precipitating factor in causing leakage of the closed duodenal stump. If transient, as in the case of edema, it will resolve as wound and fistula healing occur. If persistent, as with a faulty anastomosis, it may seriously interfere with wound and fistula healing and necessitate a dangerous and difficult secondary operation.

Although the aforementioned management of a leaking duodenal stump with subsequent duodenal fistula has to some degree diminished its dangers it has not by any means removed them completely. Therefore, every effort to prevent duodenal stump leakage will be thoroughly worthwhile.

Believing that most duodenal stump leakage occurs in those stumps where the surgeon mistrusts the closure at the time it is done, it is suggested that whenever the integrity of the closure is open to the slightest question, the surgeon abandon the effort to close it or remove the unsatisfactory sutures and resort to a small catheter in the stump held in place by a purse-string suture and attached to a suction pump. The catheter will not usually serve to remove very large amounts of fluid unless it has been placed more than 2 or 3 inches into the duodenum or unless the afferent loop is obstructed.

Suction may be decreased after 1 or 2 days and stopped after 3 or 4 days. In 6 or 7 days the catheter may be removed. Drainage of fluid after removal of the tube is usually slight and sometimes does not occur at all. It is believed that the use of this technique in cases of doubtful duodenal stump closure will be fruitful in preventing stump blowout and the serious dangers which attend it. The following case is cited.

Case 1. W. W. H., a 73-year-old man, underwent a satisfactory subtotal gastrectomy (three-fourths) for duodenal ulcer May 3, 1956. The Hofmeister type retrocolic gastrojejunal anastomosis was employed satisfactorily. The duodenal stump closure was difficult because of inflammatory infiltration and therefore not entirely satisfactory. Closure over a catheter was considered but was discarded. Subsequent events showed this to have been an error in judgment. For 7 days following operation convalescence was smooth; then nausea and vomiting occurred. That the strain of vomiting blew out the duodenal stump, was considered. The rapid development of fever and signs of peritoneal irritation seemed to substantiate the diagnosis and the next day, the 8th after gastrectomy, the wound was opened, duodenal stump leakage verified, and sump drainage instituted. Administration of prodigious amounts of fluids and electrolytes were necessary at first. Convalescence was stormy but the patient recovered completely and has had a good result from his gastrectomy. The use of a tube in closing the duodenal stump would probably have prevented the blowout; but having occurred, prompt surgical intervention saved his life.

INTERNAL HERNIA

Herniation beneath the afferent loop of the gastrojejunal anastomosis is an uncommon but interesting and important complication (figs. 2–4). In 1955 the essayist and associates[4] reported 4 cases encountered in the University of Virginia Hospital. Of these, 2 had undergone subtotal gastrectomy with retrocolic gastrojejunostomy for benign peptic ulcer; one 4 months before, the other over 1½ years before. A search of the liter-

FIG. 2. Internal herniation beneath short afferent loop of retrocolic gastrojejunostomy, left-to-right anastomosis. From Ann. Surg., *141:* 759, 1955.

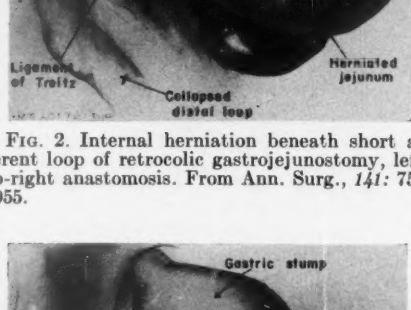

FIG. 3. Two openings through which internal hernia may occur; subtotal gastrectomy with retrocolic left-to-right gastrojejunostomy. From Ann. Surg., *141:* 759, 1955.

ature indicated that about 70 similar cases had been reported; 55 with retrocolic, 15 with antecolic anastomoses.

The clinical characteristics of the condition are those of acute upper small bowel obstruction and may be perhaps best shown by describing a typical case.

Case 2. H. G. N., a 65-year-old man, entered the University of Virginia Hospital December 5, 1952, complaining of severe upper abdominal pain of 30 hours' duration. The pain had appeared rather suddenly. Nausea and vomiting had been severe and persistent. The only pertinent history otherwise was that of a subtotal gastrectomy, with a left-to-right retrocolic gastrojejunostomy for a large but benign gastric ulcer, made by the author April 23, 1951, slightly more than 19 months previously.

Examination revealed a very tender abdomen with some muscle rigidity. There was no distention, and no peristalsis was audible. Laboratory studies showed no abnormality. Roentgenograms of the abdomen showed only traces of air in the stomach and large bowel, with none in the small bowel.

Because of experience with a previous case, the diagnosis, internal hernia through the ring formed by the short afferent loop, was made and immediate operation performed.

The operation was done by the author December 5, 1952, under subarachnoid block anesthesia. The gastrojejunal anastomosis itself was found to be normal, but the efferent loop followed by a considerable part of the small bowel had passed from right to left through the ring formed by the short afferent loop and the posterior parietal perito-

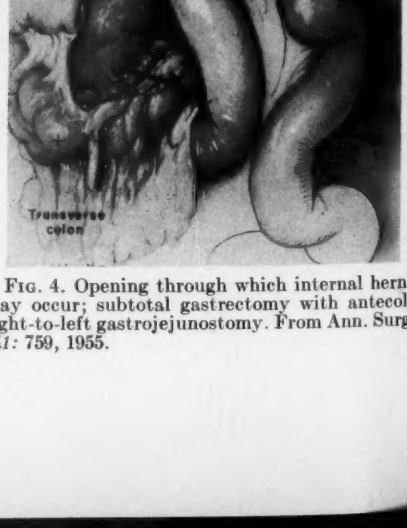

FIG. 4. Opening through which internal hernia may occur; subtotal gastrectomy with antecolic right-to-left gastrojejunostomy. From Ann. Surg., *141:* 759, 1955.

neum, and the consequent herniation was associated with partial strangulation and complete luminal obstruction. The herniated bowel was readily pulled back through the ring from left to right, and the ring closed by sutures to prevent recurrence. Convalescence was uneventful and recovery complete.

Because a ring or rings are always formed in the course of making any gastrojejunal anastomosis, it is really surprising that internal hernia is so uncommon. But, uncommon as it is, it is so serious if overlooked or not dealt with promptly that it should be at least thought of in any patient who has had a gastrojejunal anastomosis and who at any time, in days, weeks or years after operation, complains of appreciable upper abdominal pain with persistent nausea and vomiting. X-ray examination with ingestion of barium may be most helpful in making the diagnosis.

Treatment is by prompt laparotomy and reduction of the hernia. Damaged gut may necessitate resection and anastomosis. Closure of the hernial ring can usually be accomplished readily, thereby preventing any recurrence of the herniation. Although the condition occurs rather rarely (2 in 361 subtotal gastrectomies by the author and only 70 collected from the literature) prevention is so easy that it might be worthwhile for surgeons to close potential hernial rings routinely, when performing gastrectomies.

THE DUMPING SYNDROME

Fortunately, the so-called dumping syndrome troubles only relatively few patients after gastrectomy. It is characterized by epigastric discomfort or nausea or both with sweating, tachycardia, and a weak or faint feeling. Some have diarrhea. The symptoms may begin a few minutes or even immediately after the ingestion of food and may last an hour or more. Many patients have noted that very sweet foods such as milk shakes are especially conducive to trouble.

The causes of the symptoms are not clear. X-ray examinations in some patients suggest increased rapidity of gastric emptying and intestinal transport of ingested food. Various clinical and experimental studies have been made. Roberts and associates[5] believe that in gastrectomized patients the more rapid than normal passage of food into the jejunum with consequent local osmolarity changes causes a shift of plasma water into the intestinal lumen. Some jejunal distention occurs and circulating blood volume decreases. Subsequent stimulation of pressoreceptors may account for the sympathetic component of the dumping syndrome. These hypotheses are based on clinical experiments in which hypertonic solutions were introduced into the jejunum of patients who had undergone partial or total gastrectomy. Symptoms typical of the dumping syndrome were observed in the patients of the experiments.

Patients who have the dumping syndrome usually begin complaining of it very soon after their gastrectomy, when they begin taking food in any appreciable quantities. For weeks or months the symptoms may seriously interfere with efforts to restore or maintain their nutrition. Fortunately, however, most patients seem to become either less susceptible to it or else more experienced in avoiding those things that aggravate it. Probably the most helpful single measure that can be recommended to combat the symptoms is to ingest all meals as dry as possible, to avoid drinking any liquid with meals, and to rely on small meals at more frequent intervals than usual. It is probable that dry meals empty more slowly into the jejunum. In that connection it is believed that gastrojejunal anastomoses have an optimal size, if too large, rapid emptying may bring increased likelihood of the dumping syndrome. On the other hand, the too-small anastomosis may predispose to jejunal ulceration.

The following cases are illustrative of the dumping syndrome.

Case 3. E. C., 55-year-old woman, underwent subtotal gastrectomy May 10, 1947. An estimated four-fifths of the stomach was removed because of adenocarcinoma involving its mid-region. A retrocolic gastrojejunostomy of the Hofmeister type was established. Typical dumping syndrome symptoms were complained of early and persistently for a year or two but gradually became less troublesome. Now, nearly 12 years after operation, incidentally without evidence of recurrent gastric cancer, she has dumping syndrome symptoms only rarely. It is interesting, however, that she still does have them sometimes.

Case 4. L. L. S., a 69-year-old man, underwent subtotal gastrectomy for duodenal ulcer February 15, 1954. Three-fourths of the stomach was removed and a retrocolic gastrojejunostomy established by the method of Hofmeister. Postoperatively the dumping syndrome caused such severe symptomatology that nutrition fell to a dangerous

level. Gastrointestinal x-ray examination April 3, 1954, 6 weeks after operation, showed normal gastrojejunal function. Frequent meals taken as dry as possible were prescribed. It was not until 8 or 9 months after operation, however, that his symptoms showed marked improvement. Now he is not disturbed by them although he still has some occasionally.

SUMMARY

A general discussion of complications attending the operation for subtotal gastrectomy including some of the causes involved, the types found and the means useful in their prevention is presented. A more detailed discussion of duodenal stump leakage, internal hernia beneath the afferent loop of a gastrojejunal anastomosis and the so-called dumping syndrome is accompanied by illustrative case histories.

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RADIOLOGIC DIAGNOSIS OF SMALL INTESTINAL OBSTRUCTION: AN EVALUATION OF THE METHOD*

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Acute small intestinal obstruction is a common clinical entity with a significant mortality and morbidity rate. Radiographic examination of the abdomen, as one of the means of evaluating the presence or absence of such obstruction, has been utilized for many years,[2, 5, 7, 8, 11, 13, 15-17] but few attempts have been made to objectively evaluate the relative accuracy of this method of diagnosis.[4, 6, 9, 10, 14] It is proposed at this time to present part of such a study.[12]

METHOD OF STUDY

A variety of radiologic techniques, including fluoroscopy and contrast studies,[1] may at times be of help in ruling in or out small intestinal obstruction. Most commonly, however, one relies on routine filming of the abdomen, with studies preferably being obtained in at least two different projections. For the purposes of the present study, 400 examinations in which the patient received recumbent plus erect or lateral decubitus films of the abdomen were selected at random from the daily log sheets of the Department of Radiology. It was felt that this method of selecting the cases would permit a more accurate evaluation of the method, as opposed to merely selecting films on proven cases of obstruction.

The following 5-part classification was set up, covering all radiologic and clinical diagnostic possibilities as regards the presence or absence of small intestinal obstruction: (1) no evidence of obstruction; (2) indeterminate for obstruction; (3) obstruction present, mechanical type; (4) obstruction present, adynamic (paralytic) type; (5) obstruction present, mixed or uncertain type.

The official radiographic reports on these 400 examinations, dictated at the time the patients were seen, were separated according to the classification given above. Several different board certified radiologists, of which the author was one, comprised the group making these reports. The clinical charts on the patients were then reviewed, and the cases were again classified on the basis of the final, over-all clinical evaluation of the situation. It was this final clinical diagnosis which was used as the standard against which the radiologic interpretations were compared.

FINDINGS

The 400 examinations used in this study were performed on 323 different patients. In 55 instances, patients received two or more examinations, the interval between such studies varying from a day to more than a year. There were 184 men and 139 women, with a wide age distribution.

A comparison of the over-all radiologic and clinical evaluations in the 400 examinations is shown in table 1. It will be noted that in roughly two-thirds of the examinations there was no evidence of acute small intestinal obstruction, either in the final clinical evaluation or on the official radiologic interpretation. In the remaining one-third, obstruction of some type was seriously considered. At first glance these figures would suggest a very close correlation between the radiologic and clinical evaluations but, as will be shown subsequently, this is somewhat misleading. In 325 instances (82 per cent) the radiologic and clinical diagnosis agreed, whereas in 75 instances (18 per cent) the interpretation was dissimiliar.

The largest group of cases, consisting of 264 examinations, was that in which there was no evidence on final clinical analysis of small intestinal obstruction. The radiologic interpretations in this group are shown in table 2. In 243 instances, or 92 per cent of this group, the radiologic interpretation agreed with the clinical evaluation as to the absence of obstruction. In 21 instances the radiographic report disagreed, but on only 5 occasions was it suggested that definite obstruction was present. In the other 16 misses the films were interpreted as being indeterminate or inconclusive.

In 28 of the 400 examinations the final evaluation was indeterminate regarding the possibility

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TABLE 1

Interpretation of 400 examinations

Type of Obstruction	Radiologic Evaluation		Clinical Evaluation	
	No. of Cases	Per cent	No. of Cases	Per cent
No obstruction	258	64	264	66
Indeterminate	31	8	28	7
Mechanical	62	15	63	16
Paralytic	31	8	37	9
Type uncertain	18	5	8	2
Total	400	100	400	100

TABLE 2

No clinical evidence of obstruction

Radiologic Evaluation	No. of Examinations
No obstruction	243
Indeterminate	16
Mechanical	0
Paralytic	3
Type uncertain	2
Total	264
Per cent accuracy	92

of obstruction. In most of these cases the patients entered the emergency room with symptoms and initial findings raising the possibility of small intestinal obstruction, only to have the clinical picture return to normal within a few hours without a specific diagnosis having been made. In 10 instances the radiologic interpretation was also listed as indeterminate; in 8 instances it was felt that there was no evidence of obstruction and on 10 occasions the films were read as showing obstruction of some type.

In the remaining group of 108 examinations the final clinical diagnosis was that of small bowel obstruction of some type. The over-all radiologic interpretation in these 108 examinations is summerized in table 3.

In 96 instances, or 89 per cent, the radiologic interpretation agreed with the final clinical evaluation that obstruction was present. In 7 instances the films were interpretated as being negative for obstruction, and on 5 occasions the appearance was felt to be indeterminate.

A further breakdown of these obstruction cases is of interest. On 63 examinations the final clinical diagnosis was that of mechanical obstruction. The radiologic interpretation in these cases is shown in table 4. On 57 occasions, or 90 per cent, the films in this group were interpreted as showing evidence of obstruction. In 49 of the radiographic reports, representing 78 per cent of the 63 examinations, the diagnosis was that of mechanical obstruction. On 5 occasions it was felt that the films showed evidence of obstruction, but that its exact nature was uncertain, and in 3 instances a diagnosis of adynamic ileus was suggested. On 4 occasions, or 6 per cent, the films were interpreted as being negative for obstruction, and in the remaining 2 examinations the pattern was felt to be indeterminate.

The 63 examinations of clinically diagnosed mechanical obstruction represented, in all, 51 episodes of obstruction. In 39 instances there was surgical proof of the obstruction, whereas in the remaining 12 instances the clinical picture seemed clear cut. In none of these cases was there anything on the films suggesting the etiologic responsible agent.

TABLE 3

Clinical evidence of obstruction—all types

Radiologic Evaluation	No. of Examinations
No obstruction	7
Indeterminate	5
All types	96
Total	108
Per cent accuracy	89

TABLE 4

Clinical evidence of obstruction—mechanical type

Radiologic Evaluation	No. of Examinations
No obstruction	4
Indeterminate	2
Mechanical	49
Paralytic	3
Type uncertain	5
Total	63
Per cent accuracy	78

In the total group of 108 obstructions of all types there were 37 examinations in which the final clinical diagnosis was that of paralytic ileus. A survey of this group is shown in table 5. In 31 of the 37 examinations, the radiologic interpretation indicated the presence of obstruction, but in only 18 instances was a specific diagnosis of adynamic or paralytic obstruction made. The largest error occurred in the group of 8 examinations in which it was felt radiologically that the pattern indicated mechanical obstruction. On 6 occasions the films were diagnosed as being negative or indeterminate for obstruction.

Out of the 108 examinations on patients with clinically diagnosed obstruction there were 8 instances in which the final clinical evaluation was obstruction of a mixed or uncertain type. In these cases it was felt clinically that a definite obstruction existed, but that this obstruction represented either a mixture of mechanical and paralytic ileus or else the situation was so confusing that one could not with certainty differentiate between these two entities. The radiologic interpretation in this small group of cases is summerized in table 6, where it will be noted that in all 8 instances a diagnosis of obstruction was made with a specific classification of mixed or uncertain type obstruction on 5 occasions.

TABLE 5

Clinical evidence of obstruction—paralytic type

Radiologic Evaluation	No. of Examinations
No obstruction	3
Indeterminate	3
Mechanical	8
Paralytic	18
Type uncertain	5
Total	37

TABLE 6

Clinical evidence of obstruction—type uncertain

Radiologic Evaluation	No. of Examinations
No obstruction	0
Indeterminate	0
Mechanical	2
Paralytic	1
Type uncertain	5
Total	8

DISCUSSION AND SUMMARY

There are limitations in attempting a statistic analysis of the type presented in this article. The standard against which the radiologic interpretations were matched, the final clinical diagnosis, was in all probability not completely accurate in every instance. The size of this error, however, is not thought to have been great. Another difficulty is that the radiologic criteria for determining the presence or absence of various types of small bowel obstruction do not lend themselves to exact or mathematical measurements. The quantity and distribution of air and fluid within the various portions of the intestinal tract, along with the lumen diameter and mucosal patterns of demonstrable loops, are used by all radiologists in their evaluation of small bowel obstruction. There are no exact standards, however, and it has been shown that both intra-individual and inter-individual variations present real limitations in the interpretation of radiographs. It is not within the scope of this paper, to discuss either the radiologic criteria for diagnosing intestinal obstruction or the inherent limitations involved in any method of diagnosis which necessitates subjective interpretation of clinical data.[3,12]

Accepting these limitations, however, it is felt that the present study does give some objective data on the role of routine radiographic techniques in the evaluation of small intestinal obstruction.

There were 264 examinations in which the final clinical evaluation did not indicate the presence of small intestinal obstruction. In 243 of these, or 92 per cent, the radiologic interpretation reached the same conclusion. In 108 examinations the final clinical evaluation indicated that obstruction of some type was present, and in 96 of these examinations (89 per cent) the radiologist also made a diagnosis of obstruction.

Looked at another way, on 258 occasions in the present study the radiologic report stated that there was no evidence of small intestinal obstruction, and the final clinical evaluation supported this interpretation 243 times (94 per cent). In 111 instances the radiographic report stated that there was evidence of obstruction of some type, with the final clinical evaluation confirming this

opinion in 96 instances (86 per cent). On 31 occasions the radiologic report indicated that the findings were inconclusive as regards the presence or absence of obstruction. In 16 of these cases the clinical evaluation did not indicate the presence of obstruction; in 10 instances the clinical picture was indeterminate; and on 5 occasions obstruction of some type was thought to be present.

It would thus appear that a radiologist can, in a reasonably high percentage of cases, accurately evaluate the presence or absence of small intestinal obstruction on the basis of recumbent plus erect or lateral decubitus views of the abdomen. When one attempts to divide the obstructions into the various subtypes, based on their radiologic appearance, the accuracy of diagnosis decreases, but even here the radiologist can frequently make a correct evaluation of the situation. Although all errors of interpretation are of concern to the radiologist, the group of primary interest is that in which false negative reports are rendered on patients who subsequently have clinically proven mechanical obstruction. Such errors can be explained on a variety of factors. Misinterpretation of the data on the films, inadequate length of time between the filming and the onset of the obstruction and incomplete obstruction can all cause false negative or nonspecific readings. In addition, one occasionally sees cases of clinically classical obstruction, proven at surgery, in which a radiologic diagnosis of obstruction simply cannot be made on the basis of routine abdominal filming. In most of these instances the dilated small intestinal loops above the obstruction presumably are filled with fluid, rather than fluid and air, hence making their recognition difficult on routine filming.

The purpose of this article has not been to suggest that radiographic evaluation of the abdomen is the only way to diagnose small intestinal obstruction, or even to suggest that filming is necessary in every case. After all, in an obviously strangulated external hernia, the second most common cause of small bowel obstruction, one hardly needs radiographic studies to confirm the diagnosis. There are, however, many instances when the routine clinical evaluation of the acute abdomen is not so easy, and it is here that properly interpreted films of the abdomen may be of real value in ruling in or out intestinal obstruction.

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MALIGNANT MELANOMA: PROBLEMS IN CLINICAL MANAGEMENT*

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From January 1945 to January 1958, 653 patients were admitted to the University of Texas M. D. Anderson Hospital and Tumor Institute with a diagnosis of malignant melanoma. This report is concerned only with 461 whose diagnoses were confirmed microscopically in this institution. The others are not included, since the exact histologic classification remains to be determined. Of this group of 461 patients with proved malignant melanoma, 131 were treated before January 1953 and, of these, 37 (28.2 per cent) survived 5 years without obvious recurrent melanoma. The sites of the primary lesions are shown in table 1.

The history reported by the majority of these patients was similar, *i.e.*, a "mole" of many years' duration which had recently become larger and more deeply pigmented. Itching, ulceration and bleeding of the lesion were often responsible for the patient's seeking medical advice. Approximately 90 per cent of the 461 had received treatment before admission to this hospital, by biopsy, excision, cauterization, irradiation, or the application of various medications. A considerable number reported having had a small, apparently harmless mole removed by cautery or excision, no pathologic study having been made.

Whereas the history of most of these patients is similar, the behavior of malignant melanoma is often unpredictable; in fact one of the outstanding features of the disease is its protean manifestations. An interesting situation was illustrated in the case of a 54-year-old man who presented himself after having had a metastatic lymph node removed from the right groin. A few years previously he had a dark "mole" on the posterior aspect of his right leg which became infected, bled and ultimately healed. A biopsy of this area at the time of groin dissection in this hospital revealed only chronic inflammation of the dermis with slight hyperkeratosis. The patient is living and well 6½ years after groin dissection, at which time three positive lymph nodes were recovered. Since no primary lesion was found, presumably it was the "mole" on the leg which healed spontaneously.

Another patient, an 18-year-old woman, discovered a swelling in her right groin during the first trimester of pregnancy. The mass was removed 10 months later. A microscopic diagnosis of metastatic melanoma was made following lymph node biopsy and she was referred to our hospital. No further positive lymph nodes were recovered at the radical groin dissection performed in this hospital. Subsequently, 9 nevi were excised from the extremities and trunk, 1 of which exhibited slight junctional activity. Thus far, no primary melanoma has been identified, and when last observed 5 years after the groin dissection, the patient had no evidence of recurrence. The absence of a primary melanoma and the relationship of the pregnancy to the long period of survival of this patient are interesting features.

Again, a woman who was in the 7th month of pregnancy was admitted with a history of having had a mass excised from the left groin 10 days previously. The mass was first observed 4 weeks before her admission and had grown rapidly. She also reported that a mole had been excised from the calf of her left leg 7 years previously. The present pregnancy was her 4th during this 7-year period; the first three were uneventful. A groin dissection and perfusion were performed. A few weeks following delivery of a full term infant, the patient was readmitted to the hospital with disseminated melanoma involving bones, lungs, liver and subcutaneous tissues of the trunk. She succumbed 2 months after delivery. The outstanding features of this case were the failure of the disease to manifest itself throughout 3 pregnancies over a period of 7 years, and the fact that the patient died within 5 months after appearance of the metastasis during the 4th pregnancy. It will be interesting to follow the course of the infant.

Recently, we performed an axillary dissec-

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tion upon a woman who had a "mole" cauterized from the left deltoid region 15 years earlier. It recurred soon thereafter and was excised locally. The lesion was not examined microscopically, although the history was typical of malignant melanoma. She discovered a large metastatic node in the left axilla 1 month before admission to this hospital. In this case, the interval of time which elapsed between the removal of the "mole" and the appearance of metastasis is noteworthy.

Treatment. Of all primary cancers of the skin, melanoma requires the widest sacrifice of skin and underlying fat and fascia. Despite the fact that 90 per cent of these patients had received some type of therapy, the primary lesions in less than 5 per cent had been adequately excised (figs. 1 and 2). From this experience, ample excision of the primary lesion is clearly the most important aspect of treatment for melanoma. Although no rule can be established as to the amount which should be sacrificed, three factors are known to be of practical significance. (1) The tumor spreads by direct extension peripherally and in depth.[1] (2) It has a strong tendency to invade the dermal and subcutaneous lymphatics. (3) Junctional changes, often found at the periphery of a melanoma, represent unstable foci and may in themselves undergo malignant transformation.[1] Because of these three factors, wide sacrifice of skin, fat and fascia is indicated.

TABLE 1

Incidence of melanoma according to location

Location	Number	Per cent
Head and neck	146	31.7
Trunk	89	19.3
Lower extremity	89	19.3
Foot (22)		
Other (67)		
Upper extremity	81	17.6
Hand (7)		
Other (74)		
Anorectal-genitalia	10	2.1
Subungual	6	1.3
Fingernail (5)		
Toenail (1)		
Primary site unknown	40	8.7
Total cases	461	100.0

At times, local recurrences appear after seemingly adequate excision (figs. 3 and 4). These arise either from metastatic emboli lying within the cutaneous or subcutaneous lymphatics or, according to Allen,[1] from junctional foci which have been incompletely removed or have been activated subsequent to local excision. Allen believes the latter explanation is valid for the majority of recurrences. In this institution, however, the majority have exhibited the histologic features of a metastatic, rather than a primary melanoma. Anyone who has treated a fair number of patients for melanoma is aware of the inherent difficulties in controlling the primary lesion. These difficulties are greater than those encountered in treatment for other varieties of cancer of similar size which primarily affect the skin. The unique tendency of melanoma to metastasize within the skin and subcutaneous tissues presents special therapeutic problems.

We have no hesistancy in excising pigmented nevi a few millimeters or less in diameter under a local anesthetic. For tumors of one or more centimeters which are suggestive of malignant melanoma, wide excision with primary closure under a general anesthetic is preferred. This procedure is suitable for some of those on the trunk and proximal portions of the extremities. In fol-

FIG. 1. Recurrent melanoma inadequately excised previously

FIG. 2. Close-up view of arm of patient in Fig. 1. Metastatic configuration microscopically

lowing this plan, other types of lesions, such as pigmented keratoses, pigmented basal cell carcinomas (fig. 5), and benign nevi (fig. 6), may at times be excised more widely than is necessary. It is our impression, however, that the advantages of this approach outweigh the disadvantages. The margins and base of the specimen are always examined histologically as a precaution against incomplete excision. Radical excisions which require plastic reconstructive measures are not undertaken without a preliminary microscopic diagnosis of melanoma (fig. 7).

The surgical treatment for proved malignant melanoma in this institution has followed conventional lines. For the majority of primary tumors on the extremities or trunk, local excision, usually of sufficient extent to require a skin graft for closure, is regarded as the procedure of choice. For subungual lesions, amputation of the digit is performed. In our early experience, a few patients with melanomas on the lower extremities were treated by amputation or hemipelvectomy; at present, radical amputations are utilized chiefly for palliation. The treatment for those involving the skin of the head and neck consists of wide excision and, usually, in continuity neck dissection, with or without parotidectomy. Exenteration is performed for those of the eye. Abdominoperineal resection is employed for removal of anorectal lesions, and vulvectomy, generally with lymph node dissection, for those of the vulva.

Although the most important aspect of treatment concerns the primary lesion, the most controversial aspect is related to the lymph nodes. From 1948 through 1957, therapeutic node dissections were performed upon patients with clinically enlarged nodes or those who had a positive node biopsy before admission. Elective dissections, in which the nodes were clinically negative, were performed on many patients, either at the time the primary lesion was treated or 3 to 6 weeks thereafter. This practice still conforms to the majority of authoritative opinion[2, 3, 7-9] regarding lymph node dissection in the presence of melanoma, being based upon the fact that in a considerable number of cases clinically negative nodes are proved microscopically to harbor metastatic tumor. Lymphadenectomy was not carried out until the primary lesion or scar at the site of

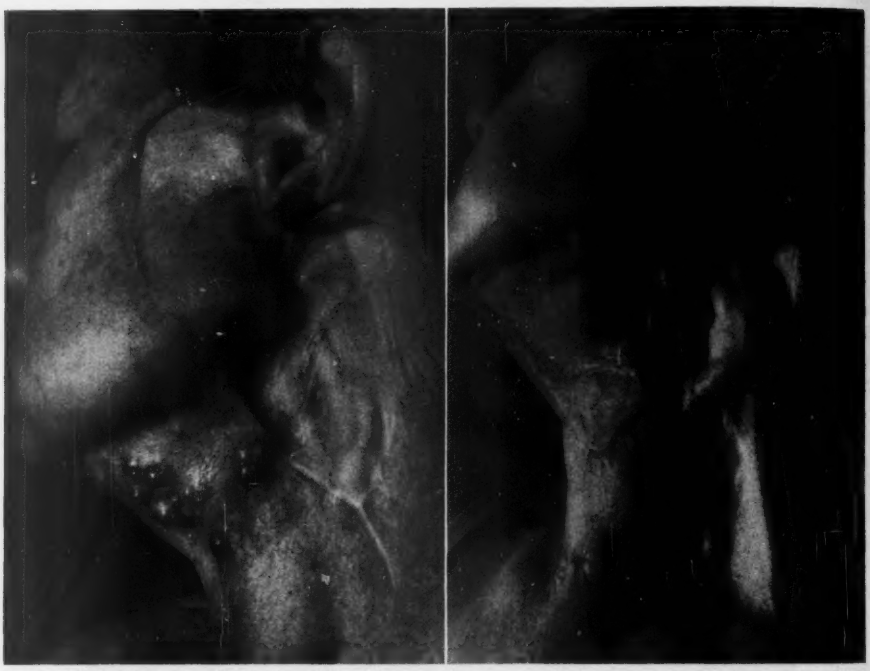

FIG. 3. Patient previously had small primary melanoma excised from preauricular region. Photograph shows regional metastatic cutaneous deposits seven months after seemingly adequate excision at this hospital (excision of scar, parotidectomy, neck dissection and skin grafting).

FIG. 4. Same patient as in Fig. 3 following extensive re-excision of cutaneous metastasis and skin grafting. Patient has no evidence of recurrence 18 months later.

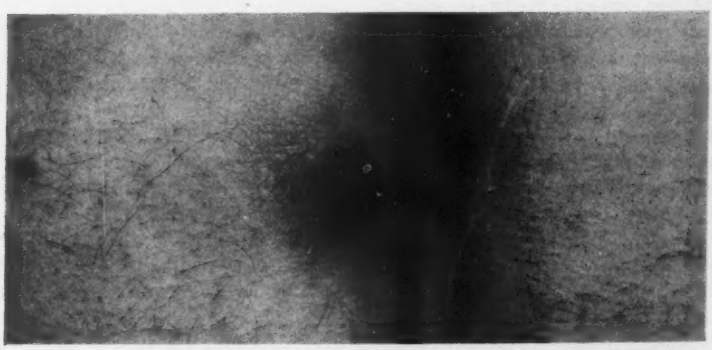

FIG. 5. Pigmented basal cell carcinoma of buttock

the primary tumor had received adequate treatment.

To determine whether this course was justified, the records of 116 patients for whom axillary or inguinal lymph node dissection was performed, between January 1948 and July 1957, were analyzed. We were particularly interested in the accuracy of our clinical diagnoses, as proved by subsequent histologic examination of the excised nodes. No attempt was made to correlate the size, depth of infiltration or histologic grade of the primary melonoma with the presence or absence of lymph node metastasis.

Of the 116 patients, 51 were men and 65 were women. The youngest was 18 years old, the oldest 76, the average age of the group being

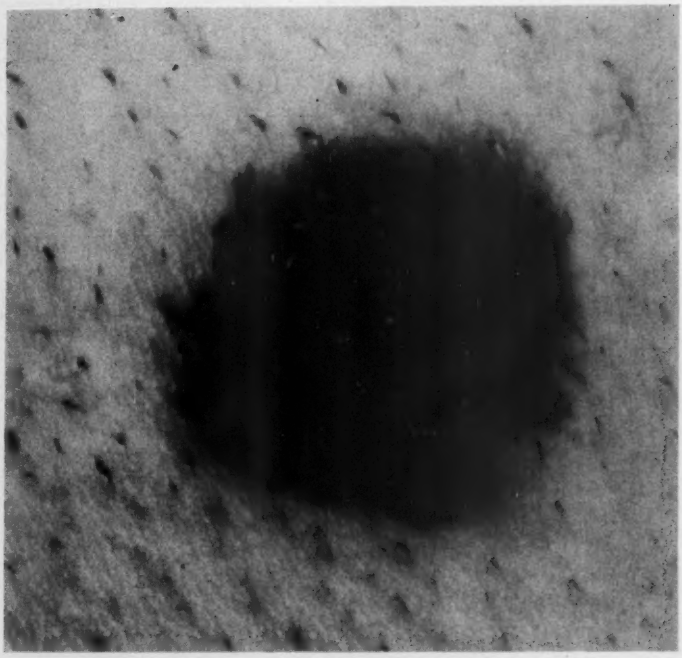

FIG. 6. Active junctional nevus, close-up view. Actual size 2.5 cm.

FIG. 7. Patient gave history of "mole" excised from arm several years previously; subsequent appearance of darkly pigmented cutaneous lesions, resembling metastatic melanoma. Multiple biopsies revealed hemangiomas. Conservative treatment.

44.5 years. The distribution of the primary lesions of patients treated by radical node dissection is shown in tables 2 and 3.

As shown in table 4, 72 (62 per cent) of the 116 patients had histologically positive lymph nodes, the incidence in the axilla and groin being 67.6 and 54.9 per cent, respectively. Our clinical impression was correct in 88.6 per cent of the 44 with histologically positive axillary nodes, and in 75 per cent of the 28 who had positive inguinal nodes (table 5).

Elective lymph node dissection was performed on 44 of the 116 patients, 21 of which were axillary and 23 inguinal (table 6). It is of interest that in 23.8 per cent of the axillary group, and 26.1 per cent of the inguinal group, metastasis was found microscopically. Thus, in approximately 1 in 4 cases of both groups our clinical impression was incorrect.

Serious postoperative complications developed only following the groin dissections. One patient succumbed on the 3rd postoperative day from renal failure secondary to hemorrhage. All patients had lymphedema of varying degrees involving the entire lower extremity; 80 per cent had minor to severe necrosis of the skin; less than 10 per cent had a hernia postoperatively. A not uncommon, and one of the most distressing complications following radical groin dissection was the development of regional cutaneous or subcutaneous metastases incident to viable tumor lying within the intervening lymphatics; 23 per cent of the patients had "tumor" complications consisting of local recurrence at the site of the primary growth, seeding in the scar of the groin dissection and/or diffuse cutaneous or subcutaneous metastatic deposits (fig. 8).

Complications following axillary dissections were minimal and, when present, consisted of skin necrosis, usually of minor degree, mild to moderate lymphedema of the upper extremity, and limitation of motion of the arm. An occasional patient had a recurrence in the scar, necessitating re-excision and skin graft.

TABLE 2

Site of primary lesion: axilla

Location	No. of Cases
Upper arm	25 (38%)
Back	17 (26%)
Anterior chest	7
Forearm	4
Subungual	3
Finger	2
Axilla	1
Unknown	6
Total	65

TABLE 3

Site of primary lesion: groin

Location	No. of Cases
Leg	16 (31%)
Foot	15
Thigh	5
Labia	3
Flank	3
Back	2
Vagina	1
Lower abdominal wall	1
Unknown	5
Total	51

TABLE 4

Lymph node data

Location	No. of Cases	Histologically Positive
Axilla	65	44 (67.6%)
Groin	51	28 (54.9%)
Total	116	72 (62%)

TABLE 5

Histologically positive nodes

Location	No. of Cases	Clinically Positive
Axilla	44	39 (88.6%)
Groin	28	21 (75%)
Total	72	60 (83.3%)

TABLE 6

Clinically negative nodes (elective node dissection)

Location	Clinically Negative	Histologically Positive
Axilla	21	5 (23.8%)
Groin	23	6 (26.1%)
Total	44	11 (25%)

FIG. 8. Multiple metastatic deposits 18 months following elective groin dissection. Lymph nodes histologically negative. Primary melanoma excised from heel. Mass in groin represents inguinal hernia.

The 5-year survivals were counted from the time of regional lymph node dissection, rather than from the time of treatment of the primary lesion. Of 37 patients who had regional dissections from 1948 through 1952, 45.9 per cent were living and well at 5 years; of the latter, 64.7 per cent had histologically negative nodes, the remaining 35.3 per cent having positive nodes.

With respect to lymph nodes, one problem deserves special mention. Frequently, patients are referred to this hospital after having a biopsy which revealed metastatic melanoma. A careful history usually reveals that the patient has received treatment for a primary lesion on the ipsilateral extremity or the same side of the trunk. In many cases, lymph node biopsy was performed under local anesthesia, the incision was poorly planned, and not infrequently the wound was seeded with tumor. The practice of obtaining biopsy specimens under such circumstances and in this manner should be condemned. In the face of known or even suspected melanoma and the subsequent appearance of regional adenopathy, a physician should not undertake nodal biopsy unless he is prepared to carry out adequate node dissection at the same operation. With few exceptions, the enlarged node represents metastasis. In these cases, we frequently perform radical node dissection without preliminary biopsy. If a biopsy is performed, however, the incision is placed in the line of the proposed incision for radical node dissection.

In view of the generally poor results of surgical treatment for melanoma, experimental and clinical studies of chemotherapy as an adjuvant to surgical treatment have been conducted in our institution during the past 6 years. As a result, our methods of treating patients, especially those with lesions involving extremities, have undergone certain changes. From the observations of Luck[6] and others, in which it was suggested that phenylalanine mustard may be more effective in the inhibition or retardation of growth of mouse melanoma than other agents, this drug has been used principally in the treatment of patients with malignant melanoma. It has been administered intravenously, intra-arterially, either by single injection or by the perfusion technique, and locally in operative wounds. The drug (30 to 50 mg.) has been given intravenously to patients with disseminated disease, for palliation. Pain from skeletal metastases has been the chief indication for employing the drug in this manner. Most of these patients have experienced some degree of relief following intravenous phenylalanine mustard, at times within 48 hours after injection. Usually this relief has been temporary.

During the past year we have been administering phenylalanine mustard intra-arterially by the perfusion technique to patients with malignant melanoma.[4, 10, 11] Large doses of the drug are delivered under high arterial oxygen tension to an isolated extremity or region of the body by means of an extracorporeal circuit (fig. 9). Two Sigma-

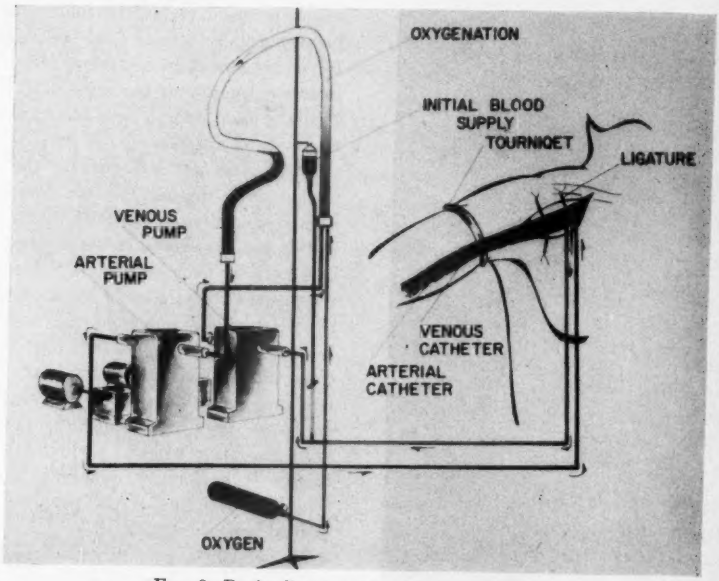

FIG. 9. Basic diagram of axillary perfusion

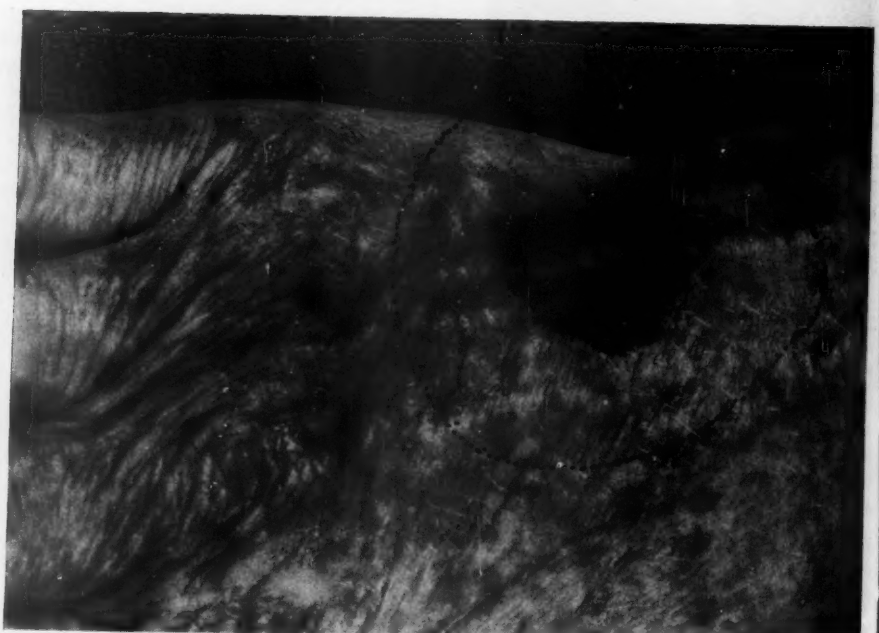

FIG. 10. Melanoma on dorsum of hand. Treatment by axillary perfusion followed by wide excision and skin graft.

motor pumps and a small, disposable oxygenator* are employed. Appropriate tourniquets are applied to prevent or minimize leakage into the systemic circulation. Regional perfusion for melanoma is currently being employed as a prophylactic measure before excision of the primary lesion, with or without lymph node dissection (fig. 10). Theoretically, this procedure offers certain possibilities, one of the most important being the destruction of viable tumor cells within the lymphatics. Impressive clinical and histologic changes have been observed in some cases. Whether or not the procedure will prove worthwhile remains to be seen. New drugs for treatment of patients with melanoma, and improvements in techniques of perfusion are being investigated.

SUMMARY

1. A brief review of 461 proved cases of malignant melanoma is presented.

2. Adequate excision of the primary lesion is the most important factor in surgical management.

3. The problem of regional lymphadenopathy is discussed, and our experiences with radical axillary and inguinal lymph node dissections from January 1948 to July 1957, is reviewed.

4. The chemotherapy program employed for malignant melanoma in this institution is described.

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ADRENALECTOMY IN THE TREATMENT OF ADVANCED BREAST CANCER

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In 1896, Beatson[1] observed regression of mammary cancer after oophorectomy. Since that time it has been well demonstrated that certain cancers from mammary epithelium retain their dependency on hormones and are influenced in growth by castration. Until 1951, surgical castration and administration of sex steroids constituted the primary therapeutic measures for combating metastatic carcinoma of the breast. Since oophorectomized patients with mammary cancer often continue to excrete estrogen in the urine, and since the adrenal glands are a source of this hormone, the combination of adrenalectomy with oophorectomy seems reasonable. All sources of sex steroids would thus be eliminated.

SELECTION OF PATIENTS

Which lesions will definitely be benefited by adrenalectomy cannot be accurately predicted. Patients in whom estrogenic activity remains would be expected to respond most favorably, but this is not always the case. Until finite criteria are established for this extensive operation, it should be reserved for patients with advanced, otherwise hopeless disease and should always be accompanied by close postoperative observation. Certain evidence has been accumulated to aid in predicting response of the patient to adrenalectomy.

Histology of primary tumor. According to Dao and Huggins[5] adrenal responsive tumors can be identified histologically. In their experience, the most responsive tumors consist of microscopic spheroids in which the lumina of the malignant acini have a lining that is one cell in thickness. Among 38 of their patients who were improved by adrenalectomy, 28 had adenocarcinomas. Duct cell carcinoma was rarely affected by this operation, and undifferentiated carcinoma was never observed by Huggins to be benefited. The presence of a well differentiated carcinoma is considered by Galante and co-workers[10] as an excellent prognostic criterion. Cade[3] does not consider the response to adrenalectomy predictable on the basis of cellular pattern since he has noted successes and failures of the operation in all histologic types. We agree with Clark and White,[4] Raven,[11] and Strode and Burgess[16] that it is not possible to predict with certainty from the cellular pattern of the growth which lesions will be benefited by adrenalectomy.

Hormone sensitivity tests. Emerson and associates[9] performed a sex hormone sensitivity test in an attempt to predict which patients with mammary cancer and osseous metastases might benefit from adrenalectomy. The metastases were considered to be hormone dependent if urinary excretion rose, or if symptoms became aggravated after a 3-day course of stilbesterol. If the urinary excretion of calcium was sharply curtailed after 2 weeks' administration of cortisone, the cancer was considered to be dependent on adrenal sex hormones and adrenalectomy was carried out.

Hormone therapy and castration. Theoretically, women of premenopausal age who have obtained transient relief from oophorectomy but have subsequently experienced recurrence of the disease would seem to be the most suitable candidates for adrenalectomy. Clinical experience thus far supports this theory. Remission after castration of the premenopausal patient is considered by Randall and co-workers[14] to be one of the most reliable indications of a favorable response to adrenalectomy. Benefit from administration of testosterone or cortisone was noted by these investigators as a likely indication of improvement after adrenalectomy. Cade[3] has reported a greater frequency of response to adrenalectomy in those women who did respond to administration of hormones.

PREOPERATIVE AND POSTOPERATIVE CARE

The patient with advanced mammary carcinoma who has to undergo bilateral adrenalectomy should of course have a thorough preoperative evaluation. Postoperative development of adrenal insufficiency should be avoided by adequate replacement therapy. Development of overhydration and its possible attendant pulmonary edema

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should be combated by limiting the intake of fluids on the day of operation and thereafter. In the absence of profuse hemorrhage, 500 ml. of blood are usually sufficient during the operation. When hypotension develops postoperatively, intravenous injection of 100 mg. of hydrocortisone will usually correct it. Vasopressors may be necessary to restore blood pressure to satisfactory levels. Adequate preoperative preparation of the patient will prevent shock that could result from the sudden removal of the adrenal glands.

Replacement therapy. Cortisone acetate is slowly absorbed by the intramuscular route; therefore, 200 to 300 mg., in divided intramuscular doses, should be given on the day preceding operation. The dose is gradually diminished until, by the 5th or 6th day after operation, a maintenance oral dose of 50 mg. has been reached. A more recent preparation, hydrocortisone sodium succinate, may be used as replacement therapy.[10] Given intramuscularly, the succinate is rapidly absorbed so that injection of steroid before the operation is unnecessary.

Desoxycorticosterone acetate may be used immediately before and after operation. It is particularly valuable in the presence of orthostatic hypotension and in patients whose sense of well being is not improved by cortisone. Most adrenalectomized patients can be maintained adequately by cortisone alone, administered orally.

The subjective state of the patient is the most sensitive criterion of an adequate maintenance dose of cortisone. Weakness, loss of the sense of well being, and anorexia rapidly develop when replacement therapy is inadequate. Patients are able to tolerate mild stress fairly well with the usual maintenance dose of cortisone, 25 mg. twice daily, and additional salt when indicated. Larger doses of cortisone are required in the presence of severe infection, trauma, or subsequent surgical intervention. The intravenous route should be used when an acute crisis occurs.

Operative technique. A spinal anesthetic may be used, although endotracheal anesthesia was used for all personal cases. If both oophorectomy and adrenalectomy are to be done, the abdomen is opened through a short, low incision, the ovaries are removed, and the wound is repaired. The adrenal glands are removed through flank incisions with resection of the 11th or 12th rib. Removal of the right adrenal gland is technically more hazardous because of its close approximation to the vena cava. It is imperative that the adrenal gland itself not be grasped, lest its removal be piecemeal and incomplete and, therefore, totally unsatisfactory. If two stages are preferred, removal of the ovaries and one gland may be accomplished first, followed by removal of the other gland 7 to 10 days later.

TABLE 1

Treatment of advanced breast cancer by adrenalectomy (934 collected cases and 25 personal cases)

Author	Date of Report	No. of Cases	No. of Remissions	No. of Postoperative Deaths
Randall and associates[14]	1959	155	54	7
Taylor and associates[17]	1956	58	16	8
Pyrah[12]	1958	75	39	8
Cade[3]	1957	136	54	8
Galante and associates[10]	1957	79	29	5
Delarue[6]	1955	32	13	5
Dao and Huggins[5]	1955	100	41	5
Hellstrom and Franksson[11]	1958	124	67	3
Raven[15]	1956	44	18	8
Rabwin and associates[13]	1956	10	3	0
Clark and White[4]	1956	36	15	1
Bartels and Fager[2]	1957	10	4	0
Eckert and associates[8]	1956	30	9	6
Douglas[7]	1957	45	20	3
Parsons and Blackshear	1959	25	10	1

RESULTS

Only those patients with far advanced, severely painful disease who had failed to obtain any relief from all forms of therapy, and who faced an undeniably hopeless prognosis were subjected to adrenalectomy. Unequivocally beneficial results, sometimes dramatic, were obtained in 10 of 20 patients. In 5 cases it is too soon after operation for an evaluation to be made. These 25 women have ranged in age from 24 to 71 years of age. There was only one postoperative death. The mean survival time for the 10 patients who did not respond to adrenalectomy is 4.9 months. Of the 10 patients who were benefited, 4 are alive, 19, 10, 8, and 3 months after adrenalectomy. The mean survival time is 17.8 months for the 6 patients who did respond but are now dead.

SUMMARY

From a review of our own and the accumulated experience of others we have concluded that

bilateral adrenalectomy has definite, often dramatic beneficial effects in certain women with advanced metastatic carcinoma of the breast (table 1). The total number of patients who have had adrenalectomy is now large enough, the postoperative period sufficiently long, and the salvage rate favorable enough to suggest its performance whenever the prognosis would otherwise be hopeless. By no means, however, are all patients benefited by this procedure. The crucial matter, therefore, is to determine which patients will respond favorably to removal of the adrenal glands. We do not agree that one can determine from the cellular pattern of the lesions which patients will be helped by adrenalectomy. Clinical evidence indicates that the woman most apt to be benefited by adrenalectomy is one in the premenopausal age who has had a temporary favorable response to oophorectomy.

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SKIN GRAFTING AFTER RADICAL MASTECTOMY

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Radical mastectomy has been the treatment of choice in cancer of the breast for over 50 years. There is still a divergence of opinion as to what constitutes adequate cancer surgery in the operable lesion. We would like to summarize some of the current thought and to present a method of pedicle grafting which has proven a valuable addition to our operation.

It should not be necessary to emphasize our belief in carefully planned radical mastectomy as the treatment of choice in cancer of the breast. The proven value of removing the cancer bearing organ in continuity with its primary lymphatic drainage system cannot be refuted by statistical studies that encourage lesser procedures. Radiation therapy should not be depended upon to mend the faults of poor surgery. McWhirter's plan[4] of simple mastectomy and heavy radiation re-emphasizes the value of x-ray therapy in the over-all management of breast cancer, and indicates what carefully planned and vigorously executed x-ray therapy can accomplish. It is our hope that McWhirter's results will encourage some of the more aggressive surgeons to turn over their advanced cases to the x-ray therapist for what we feel is superior palliation, but will not encourage the more timid surgeon to abandon the meticulous radical mastectomy in a case of curable breast cancer.

The radical mastectomy first described by Halsted[2] included the removal of all the skin of the pendulous breast, but almost no undercutting of the skin edges. This technique necessitated skin grafting in every case. Handley[3] studied the lymphatic drainage of the breast and found that the primary drainage passed first to a subareolar plexus and then to a deep plexus that spread out over the pectoral fascia. He felt that only in advanced disease, when the deep lymphatic pathways were obstructed, did the superficial plexus beneath the skin become involved. This finding led him to advocate less wide removal of skin around the tumor. He felt that undercutting the skin deeply and removing a wider area of fascia and muscle was more important. This type of operation is the most commonly used and allows primary closure of the skin in most cases. Haagensen's[1] technique combines the undercutting of very thin skin flaps with the removal of all the skin of the pendulous breast and routine skin grafting.

Surgeons will readily admit that the final answer to the cancer problem will not be found in the removal of another centimeter of skin, or a few lymph nodes, or another rib. Until the final solution is found the clinician must constantly seek improvements in technique which will prolong survival and reduce morbidity and mortality. We believe that routine skin grafting is not necessary. Large series of cases reviewed by White,[7] Oliver and Sugarbaker,[5] and Taylor and Wallace[6] indicate that local recurrence usually means that the lesion was already advanced and incurable. Other reasons for local recurrence are implantation from the biopsy site and rough blunt dissection of the axilla and chest wall. The surgeon should bear the primary responsibility for local recurrences and recognize that either his technique is faulty or that he has operated in the presence of advanced incurable disease. Irrigation of the wound and postoperative chemotherapy, as suggested by Cole,[8] may eliminate a few of these implants.

Our present technique in a relatively favorable case of breast cancer includes the removal of 5 or 6 cm. of skin on all sides of the tumor and at least 2 cm. of skin beyond the areolar. The skin flaps are cut as thin as possible removing all subcutaneous fat for another 4 or 5 cm. The flap is gradually thickened until the midline is reached medially and the latissimus dorsi muscle laterally. Primary closure is usually possible after this extensive undercutting. We emphasize sharp dissection for the entire operation and believe that it is better to leave a little fat and fibrous tissue than to scrape the chest wall and gouge the axilla with blunt dissection. We have learned to anticipate the need for skin grafting when the patient has a thin, small breast or when the tumor is large or shows evidence of skin attachment or edema re-

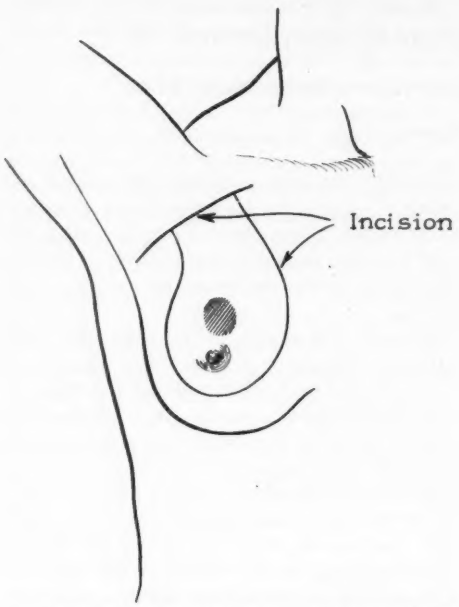

FIG. 1. Rodman incision keeps the scar from the shoulder and arm. This illustrates a minimal skin removal and primary closure should be possible.

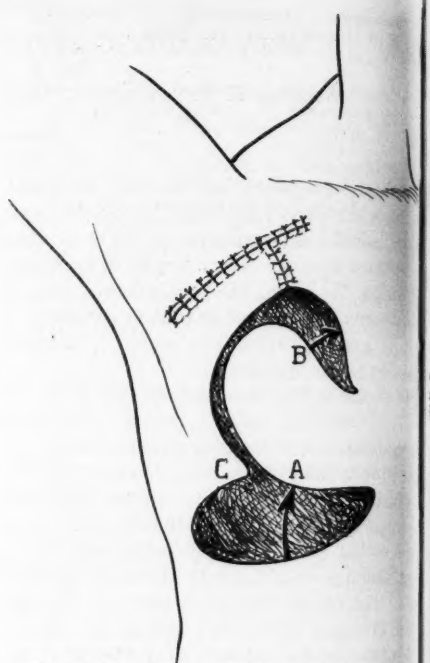

FIG. 3. The graft turned into the defect

FIG. 2. The length of the flap can be increased by using a wider base. The full thickness of skin and subcutaneous tissue is used in the flap.

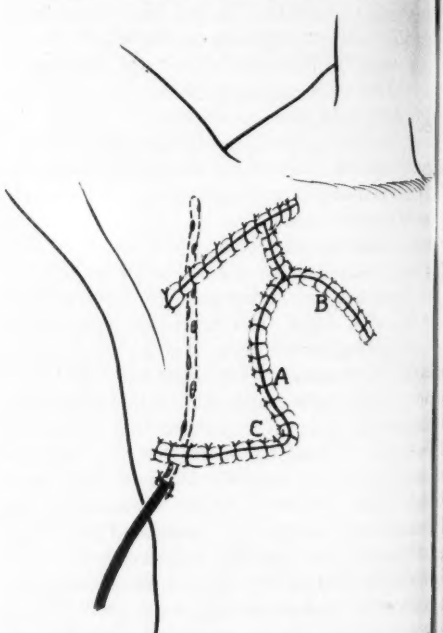

FIG. 4. Suction drain in the axilla. A small penrose drain may be needed to drain the medial portion of the wound.

FIG. 5. Photograph on the 5th postoperative day. The drains are already out. This patient had a large tumor and all the skin of the pendulous breast was removed.

FIG. 6. Grafting always necessary in the thin patient with small breasts.

quiring the sacrifice of much greater areas of skin. The use of a pedicle flap graft in these cases has proven so satisfactory that we now use it to cover the chest wall defect after internal mammary lymph node dissections.

TECHNIQUE OF PEDICLE GRAFT

When the pedicle graft is planned, a circular rather than an elliptical incision is made removing all of the skin of the pendulous breast. This leaves the skin over the lower rib cage to serve as the base for the flap to be taken from the flank. The use of a wide base makes it possible to form a flap which will reach almost to the axilla. The line of pull on this flap brings up loose abdominal skin leaving the lateral skin edges free of tension. Postoperative care is the same as in routine mastectomy. Figures 1 through 4 are a diagrammatic outline of the technique. A much larger area of skin may be removed than is depicted in the diagram.

Edwin Beer is credited with being the first to use the pedicle graft to cover a large defect after radical mastectomy. Various methods of twisting and sliding skin have since been used. The pedicle graft has never received the widespread use that such a satisfactory procedure deserves. The scar resulting from this graft is far superior to the scars resulting from a Thiersch graft, and the patient is spared the annoyance of a painful, slowly healing donor site (see figs. 5 and 6).

SUMMARY

1. In operable breast cancer, thorough, careful radical mastectomy is the treatment of choice.

2. Skin grafting need not be an integral part of every operation, but should be used in patients with small thin breasts or with large tumors and with evidence of more advanced disease.

3. A method of pedicle grafting is described which has certain advantages over the split thickness graft. The pedicle graft is especially useful in covering the chest wall defect after internal mammary lymph node dissection.

4. Local recurrence, in our experience, is usually an indication of advanced disease, and is usually accompanied by generalized metastasis.

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PHYSIOLOGIC CONSIDERATIONS IN THE DIAGNOSIS AND MANAGEMENT OF HYPERPARATHYROIDISM

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Hyperparathyroidism as a recognized disease entity has progressed over the past 25 years from a medical rarity to its present status of being not uncommonly diagnosed. Because it is so protean in its clinical signs and symptoms, it must be considered in the differential diagnosis of a wide range of diseases. In fact, the question of hyperparathyroidism should be ruled out in such diversified entities as peptic ulcer, peripheral vascular insufficiency and back pain as well as the commonly accepted clinical states of renal lithiasis and bone cysts.

PHYSIOLOGIC BACKGROUND

In order to appreciate the wide range of the clinical picture one must have a knowledge of the basic physiology of the parathyroid. The exact mode of action of parathyroid hormone is not known but it does play a large part in the regulation of calcium and phosphorus metabolism. It would appear that there is a dual action of the hormone in that it (1) raises serum calcium levels by direct action on bones and (2) lowers serum phosphorus levels through an effect on kidney excretion. Just which one of these phenomena, *i.e.*, serum calcium increase or serum phosphorus lowering, occurs first and which is the primary action of the hormone are disputed points. It is not the purpose of this paper to try to resolve that argument. However, some of the extensive experimental data which has been accumulated should be mentioned in order to point up the basic physiologic problems in the disease process. Ellsworth and Futcher[7] and subsequently, Stewart and Bowen[12] showed that the hormone, in the absence of kidneys, can act upon bone and produce electrolyte changes. Engel and associates[8] demonstrated disaggregation of glycoprotein ground substance of bone with production of mucopolysaccharides upon injection of the hormone. Crawford and associates,[5] using varying phosphorus diets, concluded that the relative constancy of phosphorus concentrations in normals is mediated by homeostatic adjustments in parathyroid activity. Predicated upon intravenous injections of the hormone, Albright and Reifenstein[1] have stated that the main action of parathyroid hormone is to cause an increased excretion of phosphorus leading to a hypophosphatemia. Experiments in regard to the primary action of parathyroid hormone on the kidney have given conflicting results. For example, Handler and associates[9] have reported that intravenous administration of the hormone caused an increased glomerular filtration rate of phosphorus with no decreased absorption but that intramuscular injection did inhibit tubular reabsorption. Sirota,[11] using simultaneous renal clearance of inulin and phosphate, demonstrated in humans that tubular reabsorption is inhibited by varying phosphate loads in pre- and postoperative cases of parathyroid adenoma. In general it can be stated that in humans the evidence is greatly in favor of the parathyroid's influencing serum phosphorus levels by inhibition of the reabsorption of phosphorus by the renal tubules. It has been shown that elevation of the circulating phosphorus levels results in parathyroid hyperplasia. Experimentally, hypophysectomy causes a decrease in serum phosphorus.[14] This raises the question of pituitary control of the parathyroids through its influence on phosphorus metabolism. The circulating calcium levels also affect parathyroid activity as seen in neonatal tetany.

It is accepted that calcium metabolism plays a major role in the manifestations of hyperparathyroidism. Calcium is present in two forms: (1) diffusable (ionized calcium plus a small part bound to citrate in an nonionized form known as the citrate-calcium complex); and (2) nondiffusable which is bound to protein as calcium proteinate. It is this calcium which is elevated in hyperparathyroidism and lends itself to labora-

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tory and differential diagnosis as will be mentioned later.

CLINICAL MANIFESTATIONS

The clinical findings associated with hyperparathyroidism may be classified under three divisions: (1) those due to bone pathology; (2) those due to renal pathology; and (3) those due to hypercalcemia *per se*. As the clinical awareness of the possibility of hyperparathyroidism has increased, the incidence of those patients with skeletal manifestations has decreased largely because of earlier diagnosis and treatment.

As far as skeletal disease in primary hyperparathyroidism is concerned, there is a generalized decalcification which may lead to superimposed cysts and tumors leading to osteitis fibrosa cystica and osteitis fibrosa cystica generalisata. The skeletal changes appear over a relatively long period of time and may show a wide range of signs and symptoms:

1. Bone pain
2. Backache
3. "Rheumatism"
4. Scoliosis
5. "Arthritis"
6. Kyphosis
7. Ruptured intervertebral disc
8. Recurrent fractures

It should be recalled that the decalcification at the ends of the clavicles is one of the earlier x-ray findings. Likewise, the subperiosteal resorption of bone of the middle phalanges has been considered pathognomonic. The usual x-ray findings in hyperparathyroidism are:

1. Crushed vertebrae
2. Ruptured discs
3. Pathologic fractures
4. Loss of lamina dura
5. Decalcification at ends of clavicle
6. Subperiosteal resorption of bone of middle phalanges
7. Bone cysts—mandible, metacarpals, metatarsals and ends of long bones
8. Metastatic calcium deposits.

The findings associated with renal pathology are much more prevalent than those associated with bony pathology at the present time. In the Mayo Clinic series reported in 1954,[3] 80 per cent of the cases had complications involving the urinary tract. The symptomatology is best described under three headings.

1. Those due to hypercalcuria and hyperphosphaturia:
   a. Polyuria
   b. Polydypsia
   c. Oliguria in the immediate postoperative period when the increased excretion of calcium and phosphorus has been eliminated.

Polyuria may also be due to tubular damage associated with nephrocalcinosis.

2. Those due to formation of kidney calculi: Here all the usual signs and symptoms of stone in the urogenital tract are encountered. In some series it has been reported that 15 per cent of recurrent calculi were due to hyperparathyroidism.[3]

3. Those due to calcium deposits in the kidney parenchyma: This is the most serious of the kidney complications. Severe impairment of kidney function is a result of this calcinosis. In many instances it may be irreversible. Hypertension is a frequent concomitant of hyperparathyroidism and although it may be due to kidney involvement it is not necessarily dependent for its presence on the renal complications but is

TABLE 1

Signs and symptoms of hypercalcemia

A.	Muscular
	1. Decreased excitability
	2. Marked hypotonicity
	3. Generalized muscular weakness
B.	Cardiovascular
	1. Cardiac arrhythmias
	2. Slow pulse
	3. Decreased Q-T interval
C.	Psychic
	1. Contrariness
	2. Maliciousness
	3. Delusions
	4. Personality changes
	5. Memory loss
D.	Gastrointestinal
	1. Nausea and vomiting
	2. Abdominal pain
	3. Dyspepsia
	4. Decreased motility
	5. Constipation
E.	Peripheral
	1. Burning sensation of skin
	2. Dryness of throat and mouth
	3. Dysphagia
	4. Pain in legs and thighs with walking

usually present initially in the disease before kidney parenchymal damage occurs.

Finally, there are a group of signs, symptoms and clinical entities associated with hypercalcemia *per se*. Noteworthy among these are hypertension, peptic ulcer diathesis and, occasionally, pancreatitis as reported by Cope and his associates.[4] It is in the systemic effects of hypercalcemia that the truly protean manifestations of hyperparathyroidism become apparent. The complaints may range from anorexia, nausea and vomiting as gastrointestinal manifestations to general malaise, weakness or personality changes (see table 1).

It is apparent from the description above that hyperparathyroidism must be kept in mind in patients who present themselves with a wide range of complaints and physical findings which include such things as: hypertension, peptic ulcer, vague gastrointestinal complaints, constipation, bone pain, kidney stone, leg and thigh pain, recurrent pancreatitis, epulis, pathological fractures, herniated nucleus pulposus, vertebral column abnormalities, dysphagia and cardiac arrhythmias.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis includes those other conditions causing a hypercalcemic state or hyperphosphaturia. As pointed out by Hills and Burr,[10] the hyperphosphaturias include "three groups of conditions: (1) the various types of hyperparathyroidism, (2) certain intrinsic selective derangements of renal tubular function, and (3) the effects of certain drugs and perhaps sometimes of humors of endogenous origin." Hypercalcemic states other than primary hyperparathyroidism include such things as vitamin D intoxication, multiple myeloma, sarcoidosis, osteoporosis, milk-alkali syndrome and malignancy metastatic to bone (even without x-ray evidence of the bony metastases). Much of the differential diagnosis rests with the proper utilization of the laboratory tests available.

LABORATORY AIDS

Classically, primary hyperparathyroidism will demonstrate an elevated serum calcium, a lowered serum phosphorus and increased urinary excretion of both calcium and phosphorus. Since most of the cases diagnosed today do not fit the classical picture *in toto* and because other entities mentioned above can approximate these findings, other laboratory tests are essential. Calcium levels may show only slight elevation and if hypoproteinemia is present, the calcium levels may be normal. With impaired renal function, phosphorus levels may be normal or elevated. An increased serum alkaline phosphatase is seen only if bony manifestations of the disease are present.

The phosphorus reabsorption index has proven to be a valuable screening test in case finding of hyperphosphaturias. The phosphorus reabsorption index (PRI) is a proportionate measure of the filtered phosphorus reabsorbed by the renal tubules. It encompasses the determination of the concentration of phosphorus and creatinine in mg. per cent in the urine and in the blood serum The index is derived by the following formula:

$$\text{PRI} = \frac{1 - [(\text{P})u\ (\text{Cr})s]}{[(\text{P})s\ (\text{Cr})u]}$$

where u and s represent urine and serum, respectively. Values in the adult generally range from 0.88 to 0.96.

The routine employed at our clinic is extremely simple and can be carried out as an office procedure: no breakfast is permitted; the patient drinks 1 quart of water on arising; the urine voided on arising and the next two voidings (at 60 and 90 minutes if possible) are discarded; the next two urines and one blood sample are then taken for analysis. Duplicate determinations are made to eliminate analytical errors. No dietary preparation is required routinely but if the determinations show a PRI below 0.88, the test is redone after a 2-day period of moderately low phosphorus diet because a high intake of phosphorus can depress the index. Besides primary hyperparathyroidism, a depressed PRI may be seen in selective lesions of the renal tubule such as vitamin D resistant rickets, Fanconi syndrome, renal tubular acidosis and secondary hyperparathyroidism associated with azotemia, rickets or osteomalacia as well as Cushing's syndrome and cirrhosis. In essence, the PRI does not distinguish primary hyperparathyroidism from other hyperphosphaturias. Also, in hypercalcemic states accompanied by an azotemia, secondary hyperparathyroidism appears and depresses the PRI. Thus, lowering of the index by no means proves the presence of hyperparathyroidism, although it calls for further studies to elucidate the cause.

On the other hand, we would be extremely reluctant to recommend surgical exploration in the face of a normal or elevated PRI.

As reported by Thomas and associates,[13] the intravenous calcium infusion test does not distinguish between the various types of hypercalcemia. On the other hand, there is reason to believe that this test may be of value in distinguishing the patient with normo-calcemic hyperparathyroidism from normal subjects.

We have found the cortisone test to be of considerable value in arriving at a decision for or against surgical exploration in hypercalcemic states. The experience of Dent and others[6] has shown that the serum calcium levels associated with primary hyperparathyroidism are not lowered by the administration of adrenal steroid. On the other hand, many patients with hypercalcemia from other causes will show a response to steroid administration with a drop in the calcium levels. We are opposed to the exploration of any patient in whom cortisone administration has caused a drop in the serum calcium.

The determination of the spinal fluid calcium level has been thought to be of possible value in the differential diagnosis of hypercalcemia. Whereas in many of the hypercalcemic states the increased calcium levels are due to diffusable calcium, the calcium increase seen with a parathyroid tumor is said to be largely due to calcium proteinate (or nondiffusable calcium). As a result, on theoretical grounds, one would expect the spinal fluid calcium to be increased in many of the other conditions causing hypercalcemia but to remain within normal range with hyperparathyroidism.

Table 2 shows the essential laboratory data on a representative group of surgically proven parathyroid tumors (studied in conjunction with Dr. Gorman Hills). One case, E. B. is worthy of further comment. This case is being reported in detail elsewhere but represents a proven case of coexisting hyperparathyroidism and sarcoidosis. Sarcoid can give many of the same clinical and laboratory findings as hyperparathyroidism including hypercalcemia. This patient showed a hypercalcemia, hyperglobulinemia, splenomegaly and anemia.

The phosphorus reabsorption index was low. Despite arguments to the contrary, when the cortisone test failed to lower the serum calcium level, surgical exploration was carried out and a parathyroid adenoma found. Sarcoidosis was proven subsequently when the spleen was removed 2 weeks after the cervical exploration and showed, microscopically, the typical findings of sarcoid.

TABLE 2

Laboratory data (preoperative) on hyperparathyroid patients, Jackson Memorial Hospital, 1957–1958

Patient	Serum Chemistries			Urine Ca (low Ca, low P diet)	PRI*
	Ca	P	Alkaline Phosphatase		
	mg. %	*mg. %*	*B.U.*	*mg./24 hrs.*	
U. P.	15.4–16.4	1.2–2.3	9.9–13.7	300	0.78
M. H.	11.8–13.3	2.5–2.8	2.5– 4.4	320	0.77
Z. W.	11.7–14.4	3.3–3.9	1.9– 3.9	200	0.68
E. B.	14.2–15.1	2.5–3.2	4.4	400	0.70
M. B.	13.2–14.5	1.4–2.4	7.2– 9.0	410	0.72
					0.78

* PRI, phosphorus reabsorption index.

SURGICAL MANAGEMENT

The preoperative preparation of a patient with hyperparathyroidism is essentially the same as for any major procedure. The patient should be in the best possible general condition. The operation itself is planned electively for the time when the homeostatic equilibrium of the patient is at an optimal state. Fluid and electrolyte balance must be obtained.

In general, a meticulous dissection must be carried out using the same approach and exposure employed for a thyroidectomy. Division of the strap muscles is mandatory. As bloodless a field as is possible of attainment is a necessity. Small hematomas can, initially, be confused with a parathyroid tumor and may obscure visualization of a small adenoma. Care must be taken not to injure the recurrent laryngeal nerves. Even if a tumor is found, all the neck area from the carotids bilaterally, the anterior and posterior surfaces of the thyroid lobes, the retrotracheal and paraesophageal areas and the region from the superior through the inferior thyroid lobes must be searched carefully. Glands are occasionally found in the carotid sheath or behind the esophagus. Multiple adenomas are found in about 10 per cent of the cases. In general, the parathyroids lie along the axis of the inferior thyroid arteries.

They may be encapsulated within the thyroid gland itself. Primary hyperplasia rather than adenoma may be the cause of the hyperparathyroidism in about 10 per cent of the cases. If diligent and meticulous dissection of the neck fails to produce the tumor or hyperplastic glands, careful finger palpation retrosternally may locate the adenoma in the superior mediastinum. If palpable, such substernal adenomas may be delivered into the neck in much the same fashion as a substernal thyroid. As in the case of a thyroid, this is a relatively safe procedure, since the blood supply is usually from the inferior thyroid artery and it courses downward into the retrosternal area with the tumor. If exploration of the neck and substernal area from the cervical incision is nonproductive, a sternal splitting procedure with exploration of the mediastinum is mandatory. Whether this latter procedure is carried out at the same sitting as the neck exploration, or as a second stage procedure depends upon many factors. Among these are: the condition of the patient, the duration of the initial procedure and the cooperation of the patient. This latter factor may be of prime importance. Some patients, due to the psychic manifestations of their disease, will refuse a second operation. In those instances, sternal splitting at the initial operation is the only possible course of action.

Postoperatively, the management of a parathyroid patient is largely one of strict attention to fluid and electrolyte balance along with prevention or early recognition of potential complications. If adequate exposure and meticulous technique are employed, permanent injury to the recurrent laryngeal nerves should not occur. However, dissection and mobilization may produce temporary edema of the nerve, resulting in temporary paralysis of the vocal cord. If this occurs bilaterally, a temporary tracheostomy will be required. Undue trauma in the retrosternal exploration could cause a break in the pleura with resultant pneumothorax. Oliguria often occurs after the removal of hyperfunctioning parathyroid tissue. The parathyroid hormone has a diuretic effect. Sudden decrease in its circulating

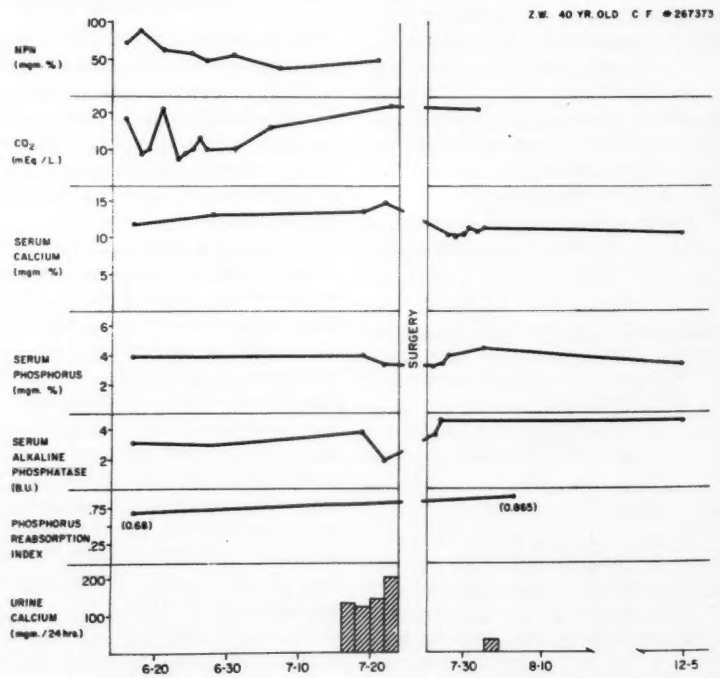

FIG. 1. Effects of removal of a parathyroid adenoma in hyperparathyroidism with azotemia and acidosis.

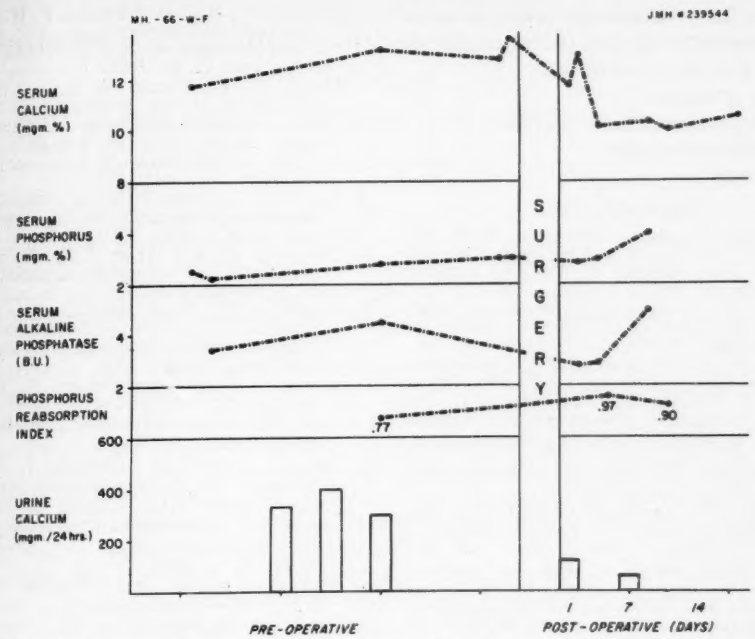

FIG. 2. Effects of removal of a parathyroid adenoma in hyperparathyroidism without bone disease (low phosphorus diet throughout).

levels may cause decreased urinary excretion. Intravenous fluid administration will counteract this tendency in the early postoperative period. Although oliguria is one of the earliest clinical indications of cure of the hyperparathyroidism, it may not occur if there has been previous impairment of renal function.[2]

There is danger of an abrupt decrease in the circulating calcium levels. Not only has the removal of calcium from bony deposits been halted but there is a rapid reversal of the process toward redeposition of calcium. In fact, calcium may be literally gulped from the circulation leading to the danger of the development of tetany. In patients with markedly demineralized skeletons, the postoperative routine employed at the Jackson Memorial Hospital is to supply the patient with 60 cc. of 10 per cent calcium gluconate intravenously for a period of several days. During this same period, 100,000 units of vitamin D are given orally, daily. The patient is also given 12 gm. of calcium lactate daily postoperatively. After the intravenous calcium gluconate has been discontinued, the vitamin D dosage is dropped to 50,000 units daily. The duration of the calcium gluconate administration rests primarily upon the extent of skeletal involvement in the hyperparathyroid process.

Figure 1 shows the typical laboratory data pre- and postoperatively in a parathyroid adenoma with acidosis and azotemia. In contrast to this, figure 2 shows the preoperative and postoperative course in an adenoma without bone disease but on a low phosphorus diet throughout the management.

SUMMARY

The clinical manifestations of hyperparathyroidism cover such a wide range of signs and symptoms that it must be considered in the differential diagnosis of renal, cardiovascular, peripheral vascular, gastrointestinal and skeletomuscular complaints.

The major manifestations may be grouped into those due to (1) skeletal involvement, (2) renal pathology and (3) hypercalcemia *per se*.

The phosphorus reabsorption index, cortisone suppression or failure thereof, and the spinal fluid calcium determinations, along with the usual serum and urine determinations of calcium and

phosphorus, are of considerable value in earlier detection and in the decision to explore patients suspected of parathyroid adenoma.

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PREVENTION OF PULMONARY EMBOLI BY PARTIAL OCCLUSION OF THE INFERIOR VENA CAVA*

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Despite the phenomenal advances in recent years in the surgical management of many of the cardiovascular diseases and the better understanding of the related pathologic physiology, little improvement in the prevention and treatment of thromboembolic disease has been evident. There seems to be some increase in the incidence of thromboembolic disease in spite of a greater awareness of the problem, probably related in part to the increased number of people in the older age groups, and to the more common performance of operations in elderly people and other poor risk patients. Ultimately, it is hoped that more effective prophylactic measures will reduce appreciably the occurrence of intravascular thrombosis. At present, however, and probably for some time to come, intravascular thrombosis continues to be an important problem in diagnosis and management.

Most surgeons concur with their medical colleagues that anticoagulant drug therapy is usually effective in preventing pulmonary embolism and in limiting further clotting and venous damage and is the treatment of choice in most instances of venous thrombosis. This treatment is not always effective, however, and in some is strongly contraindicated, as exemplified by one who has had recent prostatic surgery. Long term anticoagulant therapy, especially, is not without danger and offers particular problems in control which cannot be met satisfactorily by many patients in medically remote areas. Although in most instances venous thrombosis is best treated by anticoagulant drugs, there remains a small percentage of patients who require other means of treatment, primarily surgical interruption of venous pathways, to prevent possibly fatal pulmonary emboli.

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Dale,[4] in an excellent review of the problem, has summarized the results of various sites of venous pathway interruptions and favors inferior vena cava ligation over the more distal sites. Certainly, if the thrombosis has extended proximal to the superficial femoral vein, the greater protection against repeated embolization and the decreased associated postoperative morbidity afforded by ligation of the inferior vena cava, makes caval ligation more preferable than a more distal ligation. If one could be certain that venous thrombosis existed only in the lower leg or in the superficial femoral vein distal to its junction with the deep femoral vein, then bilateral superficial femoral vein ligation would be preferred, but of this one can practically never be certain. Evidence of this is the frequency of recurrence of pulmonary embolism following superficial femoral vein ligation as reported by Anlyan and associates,[1] Ochsner,[8] Ravdin and Kirby[11] and Dale.[4]

Ligation of the inferior vena cava is effective in preventing further episodes of pulmonary emboli as indicated by numerous reports including those of Northway and Buxton,[7] Thebaut and Ward,[15] Veal and associates,[16, 17] Shea and Robertson,[13] Poer,[9] Zollinger and Teachnor,[18] Pratt,[10] Kirtley and associates,[5] Bowers and Leb[2] and Dale and associates.[3] However, most of these authors concur that some degree of edema is very common and that leg pain, varicosities and ulcers occasionally occur particularly in those patients who are unable for one reason or another to care for their lower extremities optimally following ligation of the inferior vena cava. Several reports indicate that careful management of cooperative patients minimizes these postligation sequelae. All agree that, in carefully selected patients, inferior vena cava ligation is indicated as a life saving procedure, even though the sequelae may be considerable.

Persistent or recurrent venous pathology, seen frequently with postligation edema and ulceration, has been implicated by some as the cause of these undesirable sequelae instead of the caval ligation. It seems logical that caval occlusion by

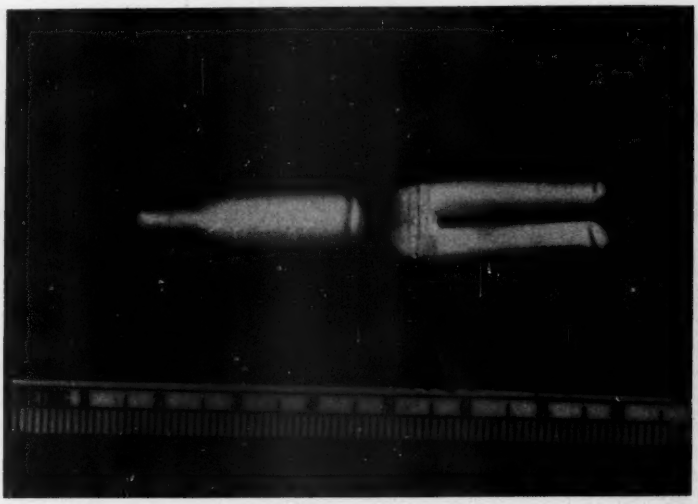

FIG. 1. Teflon clip shown in two views, with a gap of 1.0 mm. between the prongs. Clip is slipped over the vena cava from its lateral aspect and a cotton suture is tied loosely into the grooves near the medial tips to prevent the clip from slipping off of the vena cava.

its resultant increased venous pressure and venous stasis should promote recurrent thrombosis and thereby be partially responsible for the unpleasant after effects.

This possibility that a permanently occluded inferior vena cava may contribute, either directly or indirectly, to the discomfort of these patients has prompted the search for some means of interrupting the vena cava other than by permanent ligation. Streuter and Paine[14] and Dale and associates[3] have approached this by occluding the vena cava with a ligature of catgut, which in most instances later resorbs and allows the vena cava to reopen. The time and degree of reopening is not precisely predictable however and the need for vena cava interruption in some would probably be permanent instead of temporary. Moretz and associates[6] demonstrated that satisfactory temporary occlusion could be provided by a stainless steel clip which may be left in place as long as the need for occlusion is thought to exist, after which it may be removed with the expectation of early, effective reopening of the vena cava. The following experiments indicate a marked superiority of a plastic (leucite or preferrably Teflon) clip from the standpoint of early, practically complete reopening of the cava as the clip is removed.

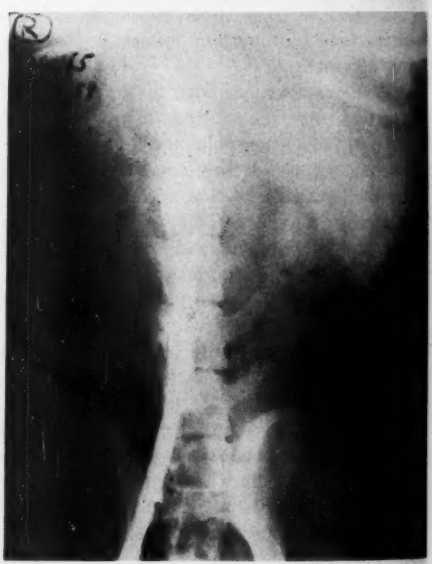

FIG. 2. Venogram taken 3 days after application of clip with gap of 1.0 mm. to inferior vena cava of dog. There is no apparent interference with the return of blood through the vena cava since the column of dye is not interrupted and no collateral veins are visible.

FIG. 3. Venogram on left was performed 10 weeks after applying a clip with a gap of 0.5 mm. to the inferior vena cava. Marked obstruction and large collateral veins are seen. The venogram on the right was taken in the same dog 3 months after the clip was removed and shows normal filling of the vena cava and a disappearance of the collateral veins.

FIG. 4. *Left*, vena cava immediately after removal of plastic clip which had been in place for 8 months. The vena cava is normally distended with no constriction at the site of previous clipping. *Right*, the same vena cava opened anteriorly shows no evidence internally of abnormality or residual of the clip occlusion.

EXPERIMENTAL RESULTS

In a series of 19 dogs, a plastic clip, made either of leucite or of Teflon (fig. 1), was placed across the inferior vena cava. The gap between the prongs of the clips varied from 0.4 to 1.6 mm., 13 being 0.5 mm. or less. These clips were removed from the vena cava after intervals of from 1 week to 12 months. Those clips with gaps greater than 0.5 mm. did not completely occlude the vena cava, whereas those with gaps of 0.4 and 0.5 mm. were essentially completely occlusive. Several findings are of importance to this study. Femoral vein pressure determinations revealed essentially no increase in pressure after applying clips with gaps larger than 0.5 mm , whereas with gaps of 0.4 mm. and 0.5 mm., there was an average increase from a preclip pressure of 30 mm. of water to 84 mm. of water. After removal of the clips, in the 9 dogs where such pressures were recorded, the venous pressure fell from an average of 126 to 80 mm. of water, usually immediately but occasionally not recorded until 3 months later.

In 2 of the 19 dogs, the vena cava had been transformed into a shrunken, fibrotic cord beginning at the clip site and extending distally for a distance of 1 to 2 cm. In no instance was a clot, new or old, found proximal (between clip and heart) to the clip. In all the remaining 17 instances, there was very good reopening of the vena cava immediately after removing the clip.

Figure 2 shows a venogram taken 3 days after application of a 1-mm. gap clip revealing an apparently nonobstructed vena cava with no visible collateral vessels. At this time the femoral vein pressure was 117 mm. of water.

Figure 3 shows venograms of dog taken 10 weeks after application of a 0.5-mm. gap clip and 3 months after the clip was removed, showing a normally filled vena cava without collateral vessels. Figure 4 shows a vena cava, immediately after removal of a clip which had been in place for 8 months. The vena cava is seen to be normally distended with no internal evidence of a clip having been applied. In this animal, the femoral venous pressure fell from 155 to 72 mm. of water immediately after the clip was removed.

In none of these animals was any evidence found of a clot having formed proximal to the clip and in only 2 of 19 was there any evidence of a clot having formed distal to the clip.

Exceedingly little reaction to the leucite and Teflon clip has been evident microscopically.

Further experiments have been carried out in dogs using Teflon clips with 1.5-mm. gaps which only partially occlude the vena cava and then subjecting these animals to the introduction of a thrombus into the veins distal to the clipped vena cava. Much difficulty was encountered in attempting to form a thrombus analogous to that seen in humans in thromboembolism, the best thrombus being formed about a No. 20 cotton thread introduced into the iliac veins and left in place for approximately 7 days. The results of these experiments, which are to be published separately, were sufficiently encouraging to prompt us to begin a cautious clinical study. Using the generally accepted indications for ligation of the inferior vena cava for prevention of pulmonary embolism, patients would be carefully chosen for the application of a Teflon clip with a gap between the two prongs of the clip wide enough to not quite occlude the vena cava but narrow enough to stop any clinically significant embolus (fig. 5).

CLINICAL EXPERIENCE

During the past 3 years, 10 patients have been seen at the Eugene Talmadge Memorial Hospital and the Veteran's Administration Hospital in Augusta, Georgia for whom the application of a

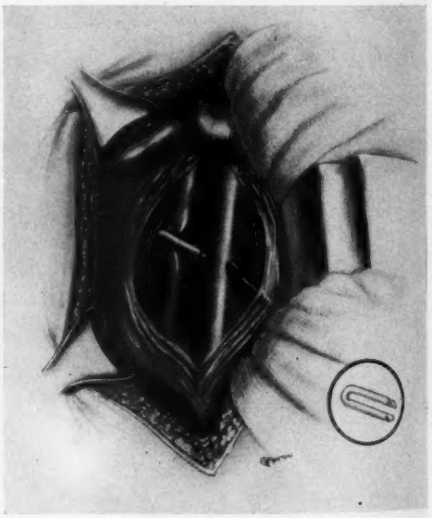

FIG. 5. Drawing of Teflon clip in place immediately after application to inferior vena cava in patient no. 9. The insert shows the clip from a different angle, with a gap of 3 mm.

TABLE 1

Summary of 10 patients with pulmonary emboli treated by partial occlusion of inferior vena cava

Patient (age)*	Primary Disease	Indications for Clip	Follow-up Period	Further Embolism	Width of Gap in Clip	Comments
			mos.		*mm.*	
1. J. F. (24)	Multiple fractures of pelvis and lumbar vert. Two pulm. emboli, last one while on full Dicoumarol therapy	Failure of anticoagulants and need for prolonged bed rest	35	None	1.6	Anticoagulants p.o. 3 mos. Elastic stockings, 8 mos. working without stockings or edema for past 2 yrs. Completely asymptomatic
2. C. H. (43)	Spontaneous phlebitis with multiple emboli while normally active, for 14 mos.	Recurrent emboli while ambulatory, after several courses of anticoagulants	27	None	2	Anticoagulants p.o. 2 mos. Elastic stockings (slight edema if support omitted), works full time
3. E. R. (36)	Spontaneous phlebitis left leg, with multiple infarctions, one after anticoagulants	Multiple emboli while ambulatory, recurrent after anticoagulants while active	27	None	2	Anticoagulants p.o. 6 wks. Extensive thrombosis, rt. leg, on 4th p.o. day. Wears elastic stockings. Not working (poor motivation, chronic complainer, no edema under hospital observation)
4. J. P. (65)	Gangrenous ileum excised with ileostomy. Developed phlebitis and multiple emboli with recurrent emboli after anticoagulants stopped	Prophylactic at time of reconstruction of ileum. Protection needed before anticoagulants could be started safely.	24	None	2	Anticoagulants started 5th p.o. day for 6 wks. Wears elastic stockings; minimal edema persists in previously phlebitic leg
5. W. S. (62)	Herniated I.V. disc. Bed rest for 6 wks. Repeated emboli while on Heparin and Dicoumarol. Cardiac decompensation	Failure of anticoagulants	1	None	1.5	Anticoagulants continued after 1st p.o. day. Cardiac decompensation. Died in 4 wks. with massive thromboses distal to clip, in superior vena cava and in jugular veins. At autopsy no thrombus between clip and heart and no recent pulmonary emboli
6. H. S. (51)	Spontaneous phlebitis with pulmonary infarcts, lung abscess and skin slough over thigh hematoma. Repeated emboli on anticoagulants	Failure of anticoagulants, prophylactic for subsequent needed surgery (thoracotomy, skin graft)	22	?	4	While applying clip, clot in inferior vena cava broke in two, but remained *in situ*. Transient mild chest pain without cyanosis or dyspnea on 7th p.o. day. Upper clot in inferior vena cava? focus for fresh thrombus. No anticoagulants. Three subsequent operations without difficulty. Wears stockings, with slight edema
7. B. J. (51)	Gastrojejuno-colic fistula with multiple pulmonary emboli	Prophylactic, protection needed for subsequent surgery when anticoagulant contraindicated.	17	None	3	No anticoagulants p.o. Two subsequent operations uneventful. Edema slight without support
8. G. W. (51)	Periarteritis nodosum diverticulitis (Sigm.) Hypertensive C.V. disease with early failure and pulmonary embolus.	While on Heparin, developed acute surgical abdomen requiring operation contraindicating anticoagulants	5	None	3	No anticoagulants p.o. Periarteritis Dx after vena cava clipping. Early edema cleared completely. Died at home without evidence of recurrent embolism, no autopsy
9. T. J. (54)	3° burn of leg. Multiple pulmonary emboli while prothrombin time prolonged without anticoagulants.	Prophylactic, skin grafts needed, contraindicating anticoagulants.	8	None	3	No anticoagulants p.o. Edema moderate early, subsiding now with elastic support. Subsequent skin grafting uneventful
10. I. C. (37)	Multiple fractures of pelvis, lumb. vert., scapula, hemopneumothorax. Pulmonary embolus while in long leg casts without recurrence after 6 days of Heparin.	Failure of anticoagulants	2	None	4	Anticoagulants p.o. 2 wks. beginning 5th p.o. day. No edema noted, but patient still in casts

* All patients were white males except patient no. 9, who was a Negro male.

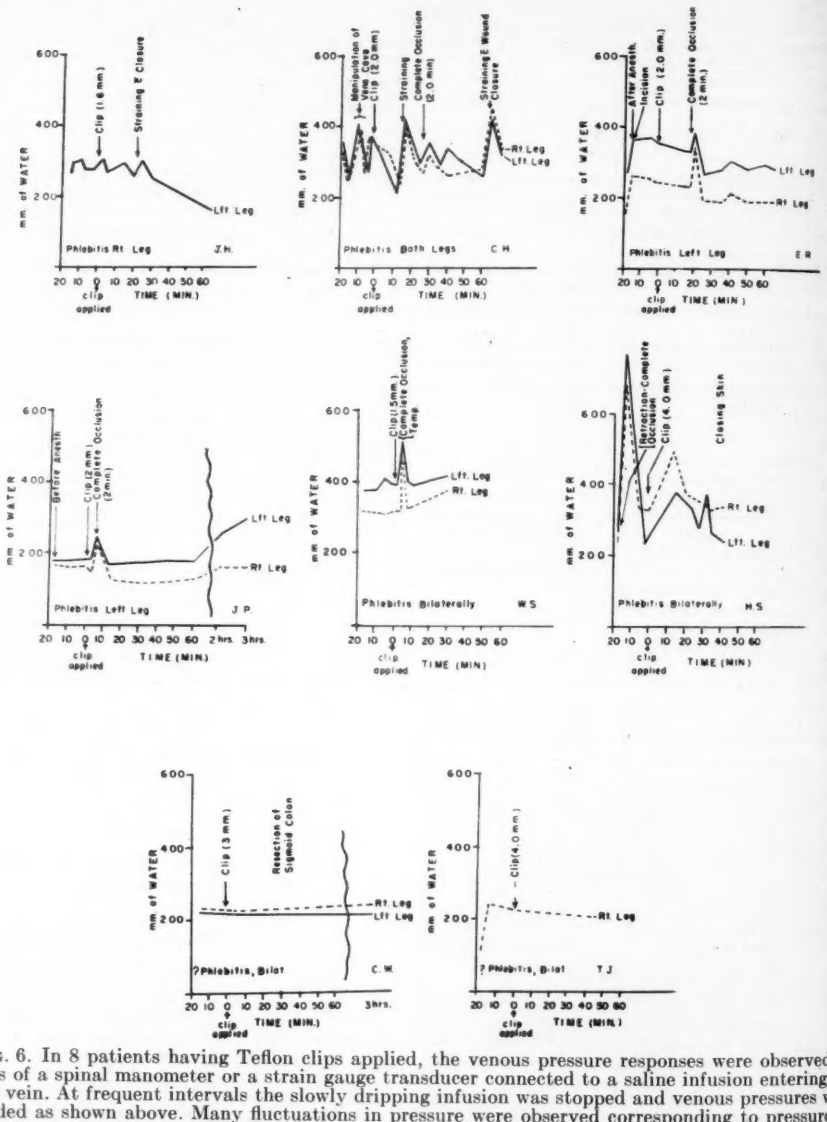

FIG. 6. In 8 patients having Teflon clips applied, the venous pressure responses were observed by means of a spinal manometer or a strain gauge transducer connected to a saline infusion entering the ankle vein. At frequent intervals the slowly dripping infusion was stopped and venous pressures were recorded as shown above. Many fluctuations in pressure were observed corresponding to pressure on the viscera and tightening of the abdominal musculature, but no significant increase in venous pressure was observed with the application of the partially occluding clip to the inferior vena cava. In each patient in whom the cava was completely occluded for a 2-minute test period a rise in venous pressure was observed.

vena cava clip was thought to be indicated. Of these, 8 have been followed for from 2 to 35 months since operation, 2 having died since the procedure, one 4 weeks after surgery while still in the hospital, the other 5 months after surgery while at home and neither with evidence of further pulmonary embolism.

The indications for vena cava occlusion in this series, shown in table 1, consist of recurrent embolization in spite of presumably adequate

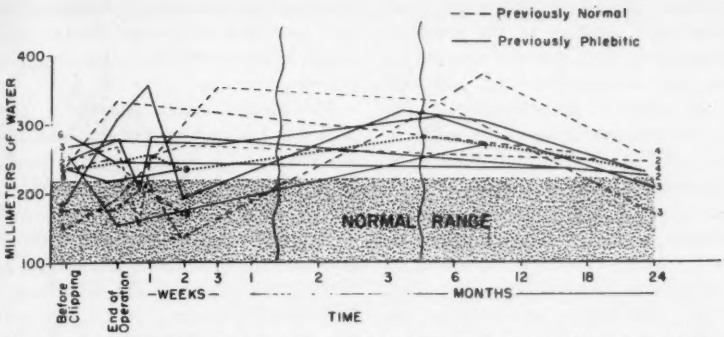

FIG. 7. Follow-up venous pressures are shown. Little difference is noted between the known previously phlebitic extremities and those thought to be normal. Average pressures are represented by the *dotted line* which is seen to remain slightly above the accepted normal range.

anticoagulant therapy (4 cases), strong contraindication to anticoagulants (5 patients, including 4 patients requiring further surgery who had had previous embolic disease), and spontaneous thrombosis and pulmonary embolism while fully ambulatory with recurrent pulmonary embolism in spite of several courses of anticoagulants (3 patients). All patients had had at least one and usually two or more pulmonary emboli and all patients except 2 had received anticoagulants previously. During this interval we have not had to treat surgically a patient with multiple septic emboli from the pelvic veins. If such were encountered, requiring surgical intervention, ligation of the inferior vena cava and ovarian veins would be recommended.

Observations on the immediate venous pressure responses in 8 patients are shown in figure 6. It can be seen that no significant early rise in venous pressure occurred, in moderate contrast to the response to complete occlusion of the vena cava which is depicted in several of the graphs.

Later venous pressure observations in these patients are shown in figure 7.

Some edema has been observed in 9 of the 10 patients, one patient being too recent (still in leg casts) for evaluation. However, excluding the 2 patients who have died and the 1 still in a cast, only 1 of the remaining 7 patients can be said to be completely asymptomatic. Of the other 6 patients, followed for 8 to 35 months, none is incapacitated by sequelae. Two have very slight edema after 27 and 17 months but wear no elastic support, one of these working full time as a guard. The remaining 4 patients use elastic stockings, in 3 of whom the support effectively controls the edema and the 4th of whom demonstrated no edema with or without support while on a forced regimen under direct observation at the Veteran's Hospital. This last patient is thought to be poorly motivated.

Leg sequelae have been acceptable in the 7 patients available for follow-up, absent in 1 after slight early edema, minimal in the remaining 6, although 1 claims some incapacitation not observable on a controlled regimen. Of the 6 patients with persistent minimal edema, 5 had edema previous to the vena cava clip, although in 1 the postclip edema is in the opposite, previously normal, leg.

DISCUSSION

At present the preferred treatment for patients with thromboembolism is adequate anticoagulation. There is general agreement, however, that interruption of the venous pathway is indicated for thromboembolism if embolism recurs during adequate anticoagulant therapy, if anticoagulants are strongly contraindicated, or if there are multiple septic emboli. There is mounting evidence that when interruption of the venous pathway is necessary in order to protect against possibly fatal pulmonary embolism, the greatest protection is afforded by interrupting the inferior vena cava rather than some more distal point in the venous system. The sequelae commonly observed after ligation of the inferior vena cava are usually not disabling and, given an intelligent and cooperative patient whose occupation does not require prolonged periods of standing, may be minimized by the proper use of external support to the legs and periodic rest periods with elevation of the

lower extremities. These sequelae are less than those observed after ligation of the common femoral veins but more than observed after superficial femoral vein interruption, and, although undesirable, are relatively unimportant in view of the greater effectiveness of vena cava occlusion in preventing pulmonary embolism than more distal vein ligations.

Postligation sequelae may be due to continued thrombophlebitis in the distal veins. It seems logical that the obstructed inferior vena cava, by increasing the venous pressure, thus increasing the size of the veins distally and reducing the speed of the flow of blood through these veins, adds to the incidence of venous thrombosis distally and, indirectly at least, leads to a greater amount of lower extremity difficulty than may be present when thromboembolic disease is managed successfully by anticoagulants alone.

The use of anticoagulants after ligation of the inferior vena cava is helpful in limiting the extension of distal venous thrombosis. In order to inhibit thrombosis effectively and to minimize further the postligation sequelae, it may be helpful in some instances to continue anticoagulants for long periods of time or perhaps indefinitely.

Recognizing the value in carefully selected patients of vena cava ligation as well as the undesirable sequelae which frequently follow, efforts to retain its value and to minimize its sequeal have been directed toward the use of temporary catgut ligatures and removable clips. These efforts appear promising.

The present study concerns a modified approach to the problem with the same aims. It was felt that a clip placed across the inferior vena cava which only partially occludes the vessel, narrow enough to stop any sizable embolus but wide enough to not materially effect the venous pressure, may offer the advantages of ligation without its sequelae. The danger of embolism with such a clip should be actually less than with complete ligation since the narrow lumen produced would be expected to stop smaller emboli than many of the large collateral veins which develop after ligation.

Experimentally, we have found that the clip does not seem to incite thrombosis, that distal venous pressures are lower than with ligation and that protection is afforded against thrombotic emboli.

On the basis of this information, a clinical trial was begun with careful follow-up studies to determine any differences in results between this method and caval ligation.

Protection against embolization is thought to be adequate, in spite of the one possible, but unsubstantiated, recurrent embolism in the pa-

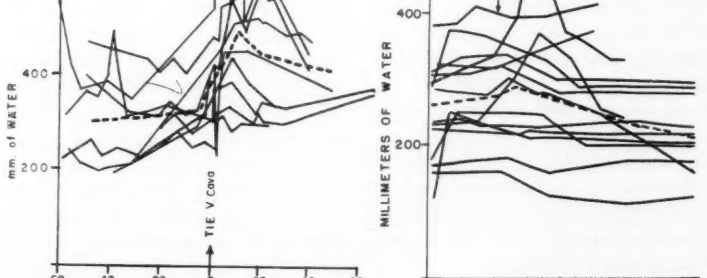

FIG. 8. On the left is a composite drawing of the venous pressure response in 6 patients to caval ligation reported by Dale.[4] On the right is a composite of the venous pressure response to partial caval occlusion, drawn from the individual responses shown in figure 6, leaving out the responses to the test period of complete occlusion. The *broken line* represents the average pressure in each series. The immediate rise in venous pressure common to complete caval occlusion is lacking with partially occluding clips.

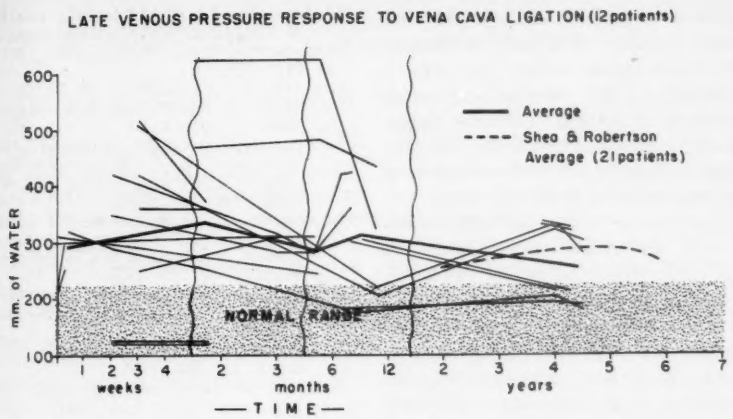

FIG. 9. The heavy, solid line represents the average follow-up venous pressures reported by Ray and Burch.[12] The heavy, *broken line* represents the pressures reported by Shea and Robertson.[13] Comparing these with figure 7, a slight difference in pressures is noted, favoring partial occlusion.

tient whose inferior vena cava clot broke in two during the application of the clip. In this instance, if embolization occurred, the most likely focus for its origination was in the clot proximal to the clip which would have been no less an inciting factor had the vena cava been ligated.

No significant increase in venous pressure distal to the clip was observed in the immediate post-clipping period, whereas with the 2-minute test period of complete occlusion, a slight rise in pressure occurred. Dale[4] in his observations on the pressure response of 6 patients with ligation of the vena cava also noted a moderate increase in pressure which is compared with the pressure response in our series in figure 8.

Late venous pressures in patients having had ligation of the vena cava are shown in figure 9, drawn from the data reported by Ray and Burch[12] and the more long term pressures reported by Shea and Robertson.[13] These are slightly higher than the venous pressures found in this series (fig. 7).

The amount of leg discomfort and edema is thought to be less than would be expected with ligation although the number of patients is too small and the follow-up period is too short for meaningful evaluation at this time. It is our impression that visible collateral vessels in the abdominal wall and leg varicosities are also less than is seen with ligation, being minimal in this series to date. No skin ulcerations have developed.

At this time, however, it is apparent that not all lower extremity difficulties will be avoided by only partially occluding the vena cava. It is evident that anticoagulants would seem indicated as soon as feasible postoperatively to prevent recurrent episodes of thrombophlebitis, whether the inferior vena cava has been only partially occluded by a clip or whether it has been ligated.

This is a preliminary report and no final evaluation of this procedure can be made until more patients have been carefully observed for longer periods of time. The results appear to be promising at present, but not so promising that the indications for surgery in the treatment of this form of thromboembolic disease should be any less rigid than they now are for ligation of the inferior vena cava.

SUMMARY

The preferred treatment for thromboembolic disease is, in general, adequate anticoagulation. Interruption of the venous pathway between the site of thrombus and the heart is needed in some instances as a lifesaving measure if anticoagulants are either contraindicated or ineffective.

In an effort to provide the protection of inferior vena cava ligation with a decrease in the post-ligation sequelae, we have used a plastic clip to interrupt the cava, first in the experimental laboratory and later in a series of 10 patients.

Experimentally, completely or partially occluding leucite or Teflon clips placed across the inferior vena cava did not seem to incite thrombosis within the cava, since no thrombus was seen proximal to the clip and in only 2 of 19 dogs was

there evidence of thrombosis distal to the clip. This is a lower incidence of thrombosis than we have observed with ligation of the vena cava. A partially occluding clip afforded protection against embolization without producing significant venous hypertension distal to the clip. Removal of the clip usually allowed a complete or nearly complete reopening of the vena cava.

In the 10 patients treated by partially occluding Teflon clips, the results were thought to be satisfactory. No further embolization was noted, with the possible exception of a questionable embolus in a patient with known clot in the vena cava at the time the clip was applied, just cephalad to the clip site. In the 7 patients with follow-up periods of from 8 to 35 months, slight early edema was noted in all, although 1 is now asymptomatic and 6 have minimal edema. Of the 6 with persistent minimal edema, 5 had edema before operation.

The early and late venous pressures in this series are compared with those reported for caval ligation.

The results of partial occlusion of the inferior vena cava in the treatment of thromboembolism seem promising, but no final evaluation is possible at this time.

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Book Review

Instrumentation in Anesthesiology. By WILLIAM H. L. DORNETTE, M.D., and VERNE L. BRECHNER, M.D. 242 pp., Lea & Febiger, Philadelphia, 1959.

This excellent volume might better be titled, "Instrumentation in Medicine." The authors have done a creditable job of surveying the gamut of measuring techniques and equipment for the reader. The introductory chapters which deal with safety precautions and basic physics of electricity are well written, adequately illustrated and sufficiently elementary to be useful even to the novice.

The whole spectrum of cardiac monitoring from simple techniques of oscultation to the complex electrocardiography and phonocardiography is covered. Although it may be deemed advisable from the standpoint of completeness, the section on electrocardiography seems somewhat redundant in view of the large number of excellent monographs on electrocardiography already available. The subsequent sections dealing with the measurements of temperature, pressure, and flow are quite complete and well presented. There is also a section devoted to the analysis of the respiratory gases and anesthetic agents. The concluding section deals with servo-mechanisms and plans for central monitoring systems.

A brief, but adequate bibliography is appended to each section. In summary, this is an excellent small volume which should be extremely useful to individuals in all fields of medicine who are interested in gaining some background in the rapidly increasing area of medical instrumentation. Although the sections on basic physics and electronics might be too simple for those with engineering background, the correlation between the basic engineering problems and the requirements in the medical application of the principles involved makes it extremely useful even to these individuals.

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